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(71) Applicant *(for all designated States except US)*: **RIBAPHARM INC.** [US/US]; 3300 Hyland Avenue, Costa Mesa, CA 92626 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AN, Haoyun** [US/US]; 7864 Paseo Tulipero, Carlsbad, CA 92009 (US). **RAMASAMY, Kanda** [IN/US]; 92 Timberland, Aliso Viejo, CA 92656 (US). **CHAMAKURA, Varaprasad** [IN/US]; 1300 Adams Avenue, #11G, Costa Mesa, CA 92626 (US). **HONG, Zhi** [US/US]; 79 Timberland, Aliso Viejo, CA 92656 (US).

(74) Agents: **RUTAN & TUCKER, LLP** et al.; P.O. Box 1950, 611 Anton Blvd., Fourteenth Floor, Costa Mesa, CA 92628-1950 (US).

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(54) Title: DEAZAPURINE NUCLEOSIDE ANALOGS AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract: Methods, compositions, and uses for various nucleoside analog libraries and library compounds are provided. Particularly preferred nucleosides include 6-C-purine nucleosides, 7,8-substituted purine nucleosides, pyrazolopyrimidine nucleoside analogs, various pyrimidine nucleosides, and triazine nucleosides, while preferred uses especially include use of such compounds as pharmacological, and particularly antiviral agents.

DEAZAPURINE NUCLEOSIDE ANALOGS AND THEIR USE AS THERAPEUTIC AGENTS

This application claims the benefit of U.S. provisional patent application with the serial number 60/350296, filed January 17, 2002, which is incorporated by reference herein.

Field of The Invention

The field of the invention is nucleoside analogs, and is especially directed towards various deazapurine nucleosides and their therapeutic use, particularly for treatment of viral infections with HCV, HRV, RSV, HIV, HBV, as well as viruses in the families of Flaviviridae, Paramyxoviridae, Orthomyxoviridae, Picornaviridae, Bunyaviridae, Arenaviridae, and Herpesviridae.

Background of The Invention

Nucleosides, and especially purine-type nucleosides and their analogs interact with many biological targets, and some nucleoside analogues have been used as antimetabolites for treatment of cancers and viral infections. After entry into the cell, many nucleoside analogues can be phosphorylated to monophosphates by nucleoside kinases, and then further phosphorylated by nucleoside monophosphate kinases and nucleoside diphosphate kinases to give nucleoside triphosphates. Once a nucleoside analogue is converted to its triphosphate inside the cell, it can be incorporated into DNA or RNA. Incorporation of certain unnatural nucleoside analogues into nucleic acid replicates or transcripts can interrupt gene expression by early chain termination or by interfering with the function of the modified nucleic acids. In addition, certain nucleoside analogue triphosphates are very potent, competitive inhibitors of DNA or RNA polymerases, which can significantly reduce the rate at which the natural nucleoside can be incorporated. Many anti-HIV nucleoside analogues fall into this category, including 3'-*C*-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, and 2',3'-didehydro-2',3'-dideoxythymidine.

Various purine-type and other nucleoside analogues can also act in other ways, for example, causing apoptosis of cancer cells and/or modulating immune systems. In addition to nucleoside antimetabolites, a number of nucleoside analogues that show very potent anticancer and antiviral activities act through still other mechanisms. Some well-known nucleoside anticancer drugs are thymidylate synthase inhibitors such as 5-fluorouridine, and

adenosine deaminase inhibitors such as 2-chloroadenosine. A well-studied anticancer compound, neplanocin A, is an inhibitor of S-adenosylhomocysteine hydrolase, which shows potent anticancer and antiviral activities.

Unfortunately, many nucleoside analogues that can inhibit tumor growth or viral infections are also toxic to normal mammalian cells, primarily because these nucleoside analogues lack adequate selectivity between the normal cells and the virus-infected host cells or cancer cells. For this reason, many otherwise promising nucleoside analogues fail to become therapeutics in the treatment of various diseases.

Selective inhibition of cancer cells or host cells infected by viruses has been an important subject for some time, and tremendous efforts have been made to search for more selective nucleoside analogues. In general, however, a large pool of nucleoside analogues is thought to be necessary in order to identify highly selective nucleoside analogues. Unfortunately, the classical method of synthesizing nucleosides and nucleotides having desired physiochemical properties, and then screening them individually, takes a significant amount of time to identify a lead molecule. Although thousands of nucleoside analogues were synthesized over the past decades, if both sugar and base modifications are considered, many additional analogues are still waiting to be synthesized.

During the last few years, combinatorial chemistry has been used to generate huge numbers of organic compounds other than nucleosides, nucleotides, and their analogs resulting in large compound libraries. If nucleosides, nucleotides, and their analogs could be made through a combinatorial chemistry approach, a large number of such compounds could be synthesized within months instead of decades and large libraries could be developed. A combinatorial chemistry approach to nucleosides may also encourage a focus beyond previously addressed biological targets. For example, in the past nucleoside analogues were usually designed as potential inhibitors of DNA or RNA polymerases and several other enzymes and receptors, including inosine monophosphate dehydrogenase, protein kinases, and adenosine receptors. If a vast number of diversified nucleoside analogues could be created, their uses may be far beyond those previously recognized biological targets, which would open a new era for the use of nucleoside analogues as human therapeutics.

The generation of combinatorial libraries of chemical compounds other than nucleosides, nucleotides, and their analogs by employing solid phase synthesis is well known

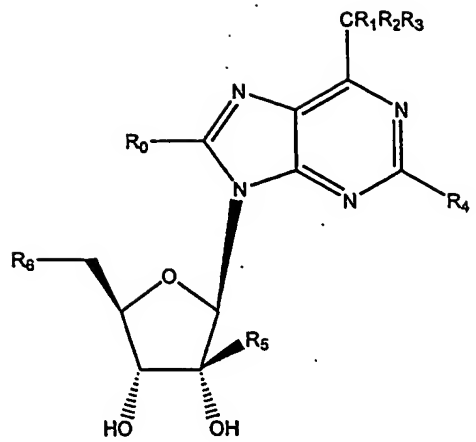
in the art. For example, Geysen, et al. (*Proc. Natl. Acac. Sci. USA*, 3998 (1984)) describes the construction of a multi-amino acid peptide library; Houghton, et al. (*Nature*, 354, 84 (1991)) describes the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery; Lam, et al. (*Nature*, 354, 82 (1991)) describes a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin. Although a combinatorial chemistry approach has been proven to work well with many types of compounds, there are numerous problems with the generation of nucleoside libraries. Among numerous other difficulties, most nucleoside analogues contain a sugar moiety and a nucleoside base, which are linked together through a glycosidic bond. The formation of the glycosidic bond can be achieved through a few types of condensation reactions. However, most of the reactions do not give a very good yield of desired products, which may not be suitable to the generation of nucleoside libraries.

Moreover, the glycosidic bonds in many nucleosides are in labile to acidic condition, and many useful reactions in combinatorial chemistry approaches cannot be used in the generation of nucleoside analogue libraries. As a result, many researchers have focused their attention to areas in pharmaceutical chemistry that appear to present an easier access to potential therapeutic molecules, and there seems to be a lack of methods for generating libraries of nucleosides and nucleotides using solid phase synthesis. Therefore, there is still a need to provide new nucleoside compounds and methods for generation of nucleoside and nucleotide libraries.

Summary of the Invention

The present invention is directed to nucleoside analog libraries, library compounds, and their methods of use. Particularly contemplated nucleoside analog libraries will include library compounds with a modified sugar portion (most preferably modified at the C2'-position) and/or a modified purine base.

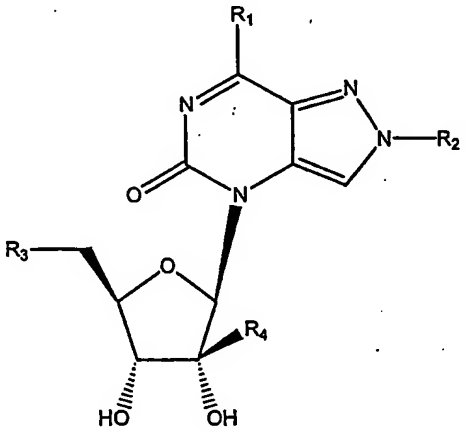
Thus, in one aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 1**



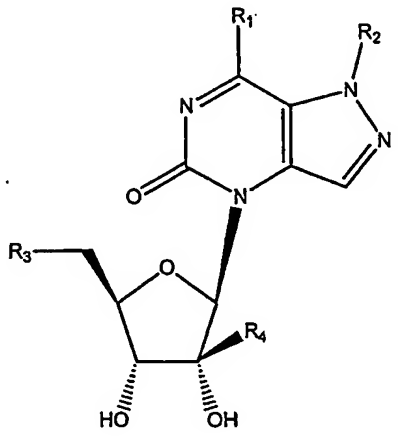
Formula 1

wherein the sugar is in D- or L-configuration; R_0 is H, halogen, alkyl, alkenyl, alkynyl, or aryl (all of which may be substituted); R_1, R_2, and R_3 are independently alkyl, alkenyl, alkynyl, aryl (all of which may be substituted), or H; and further preferred compounds include those in which R_1 and R_2 are H, and in which R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR', or alkyl-CN; R_4 is H or NH_2; R_5 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; R_6 is H, OH, phosphate, phosphonate, or boranophosphate; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

In a further aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 2A** or **Formula 2B**



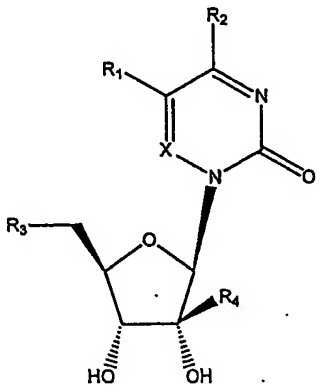
Formula 2A



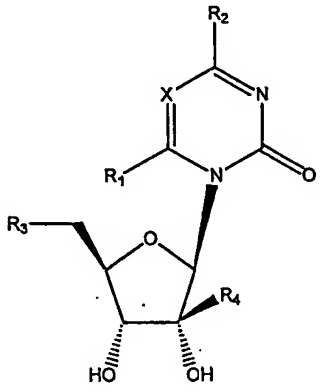
Formula 2B

wherein the sugar is in D- or L-configuration; R_1 is NR'R", ONR'R", NR'NR'R", SR', OR', or R'; R_2 is alkyl, acyl, or aryl; R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

In a still further aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 3A** or **Formula 3B**



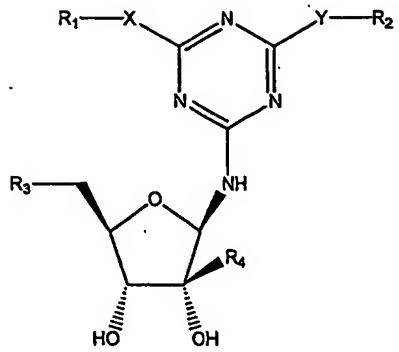
Formula 3A



Formula 3B

wherein the sugar is in D- or L-configuration; X is N or CH; R_1 is H, halogen, alkyl, or alkenyl; R_2 is NR'R", ONR'R", NR'NR'R", SR', OR', or R'; R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

In yet another aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 4**

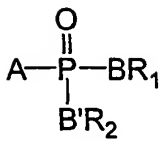


Formula 4

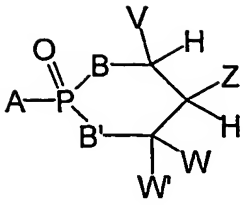
wherein X and Y are independently null, NR', O or S; R_1 and R_2 are independently NR'R", H, alkyl, alkenyl, alkynyl, or aryl (all of which may be further substituted); R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

Further contemplated compounds also include phosphorylated forms (preferably at the 5'-atom), prodrugs, and/or metabolites of the above compounds, and in especially preferred aspects, such compounds may include a moiety (*e.g.*, a cyclic phosphate, a cyclic phosphonate, a cyclic phosphoamidate, or a non-cyclic phosphate (di-) ester) that is covalently coupled to the C2'-atom, C3'-atom, and/or C5'-atom (thereby replacing the corresponding OH group), wherein at least part of the moiety may be preferentially cleaved from the compound in a target cell or target organ.

Therefore, in a further aspect of the inventive subject matter, preferred moieties will have a structure according to **Formulae M1** or **M2**, wherein A, B, B', V, W, W', and Z are defined as in the section entitled "Contemplated Compounds" below. Yet further contemplated prodrugs include SATE (S-acyl-thio-ethyl) and pivalic acid ester-prodrug forms of contemplated compounds.



M1



M2

In a still further aspect of the inventive subject matter, a pharmaceutical composition includes contemplated compounds at a concentration effective to reduce viral propagation of a virus in a patient infected with the virus (*e.g.*, HCV virus, an HRV virus, an RSV virus, an HIV virus, and an HBV virus). Contemplated compositions may further comprise a second pharmacologically active molecule, and particularly preferred molecules include a cytokine (and fragments thereof), immunomodulators, and antibodies.

Consequently, the inventors contemplate a method of treating a viral infection in a patient in which contemplated compounds are administered to the patient in an amount effective to reduce viral propagation. Viewed from another perspective, the inventors contemplate a method of reducing viral propagation in a cell infected with a virus, wherein contemplated compounds present the cell in an amount effective to reduce viral propagation.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

Detailed Description

The inventors have discovered that various nucleoside, and especially various deazapurine nucleoside analogs, may be employed as therapeutic molecules, and especially as antiviral agents (*e.g.*, against HCV).

The term "nucleoside library" as used herein refers to a plurality of chemically distinct nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs wherein at least some of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs include, or have been synthesized from a common precursor.

For example, a plurality of nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs that were prepared from a protected ribofuranose as a building block/precursor is considered a nucleoside library under the scope of this definition. Therefore, the term "common precursor" may encompass a starting material in a first step in a synthesis as well as a synthesis intermediate (*i.e.*, a compound derived from a starting material). In another example, at least one step in the synthesis of one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs is concurrent with at least one step in the synthesis of another one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and synthesis is preferably at least partially automated. In contrast, a collection of individually synthesized nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and especially a collection of compounds not obtained from a nucleoside library, is not considered a nucleoside library because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs will not have a common precursor, and because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs are not concurrently produced.

It is further generally contemplated that the complexity of contemplated libraries is at least 20 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, more typically at least 100 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, and most typically at least 1,000 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs. Consequently, a typical format of a nucleoside library will include multi-well plates or a plurality of small volume (*i.e.*, less than 1 ml) vessels coupled to each other. The term "library compound" as used herein refers to a nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog within a nucleoside library.

The term "nucleoside" refers to all compounds in which a heterocyclic base is covalently coupled to a sugar, and an especially preferred coupling of the nucleoside to the sugar includes a C1'-(glycosidic) bond of a carbon atom in a sugar to a carbon or heteroatom (typically nitrogen) in the heterocyclic base. The term "nucleoside analog" as used herein refers to all nucleosides in which the sugar is not a ribofuranose and/or in which the heterocyclic base is not a naturally occurring base (*e.g.*, A, G, C, T, I, etc.). It should further be particularly appreciated that the terms nucleoside and nucleoside analog also include all prodrug forms of a nucleoside or nucleoside analog, wherein the prodrug form may be activated/converted to the active drug/nucleoside in one or more than one step, and wherein

the activation/conversion of the prodrug into the active drug/nucleoside may occur intracellularly or extracellularly (in a single step or multiple steps). Especially contemplated prodrug forms include those that confer a particular specificity towards a diseased or infected cell or organ, and exemplary contemplated prodrug forms are described in "Prodrugs" by Kenneth B. Sloan (Marcel Dekker; ISBN: 0824786297), "Design of Prodrugs" by Hans Bundgaard (ASIN: 044480675X), or in copending US application number 09/594410, filed 06/16/2000, all of which are incorporated by reference herein.

Similarly, the term "nucleotide" as used herein refers to a nucleoside that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.). Consequently, the term "nucleotide analog" refers to a nucleoside analog that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.).

As used herein, the terms "heterocycle" and "heterocyclic base" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, and wherein the ring includes at least one atom other than a carbon atom. Particularly contemplated heterocyclic bases include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocylces may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, 7-deazapurine, 7-deaza-8-azapurine, 3-deazapurine, or 9-deazapurine).

Still further contemplated heterocyclic bases may be aromatic, or may include one or more double or triple bonds. Moreover, contemplated heterocyclic bases may further include one or more substituents other than hydrogen, and especially contemplated substituents include those referenced below. Contemplated heterocycles or substituted heterocycles are typically attached directly to nucleoside bases or sugars, but coupling of the heterocyclic base to the sugar may also include a linker moiety with at least 1-4 atoms between the heterocyclic base and the sugar.

As further used herein, the term "sugar" refers to all carbohydrates and derivatives thereof, wherein particularly contemplated derivatives include deletion, substitution or

addition of a chemical group in the sugar. For example, especially contemplated deletions include 2'-deoxy and/or 3'-deoxy sugars. Especially contemplated substitutions include replacement of the ring-oxygen with sulfur, methylene, or nitrogen, or replacement of a hydroxyl group with a halogen, an amino-, sulfhydryl-, or methyl group, and especially contemplated additions include methylene phosphonate groups, 2'-beta-methyl and/or 3'-beta-methyl groups. Further contemplated sugars also include sugar analogs (*i.e.*, not naturally occurring sugars), and particularly carbocyclic ring systems. The term " carbocyclic ring system" as used herein refers to any molecule in which a plurality of carbon atoms form a ring, and in especially contemplated carbocyclic ring systems the ring is formed from 3, 4, 5, or 6 carbon atoms. Examples of these and further preferred sugars are provided below.

The terms "alkyl" and "unsubstituted alkyl" are used interchangeably herein and refer to any linear, branched, or cyclic hydrocarbon in which all carbon-carbon bonds are single bonds. The term "substituted alkyl" as used herein refers to any alkyl that further comprises a functional group, and particularly contemplated functional groups include nucleophilic (*e.g.*, -NH_2, -OH, -SH, -NC, etc.) and electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., -NH_3^+), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof. The terms "alkenyl" and "unsubstituted alkenyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl with at least one carbon-carbon double bond. The term "substituted alkenyl" as used herein refers to any alkenyl that further comprises a functional group, and particularly contemplated functional groups include those discussed above.

Furthermore, the terms "alkynyl" and "unsubstituted alkynyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl or alkenyl with at least one carbon-carbon triple bond. The term "substituted alkynyl" as used herein refers to any alkynyl that further comprises a functional group, and particularly contemplated functional groups include those discussed above. The terms "aryl" and "unsubstituted aryl" are used interchangeably herein and refer to any aromatic cyclic, alkenyl, or alkynyl. The term "substituted aryl" as used herein refers to any aryl that further comprises a functional group, and particularly contemplated functional groups include those discussed above. The term "alkaryl" is employed where the aryl is further covalently bound to an alkyl, alkenyl, or alkynyl.

Thus, the term "substituted" as used herein also refers to a replacement of a chemical group or substituent (typically H or OH) with a functional group, and particularly contemplated functional groups include nucleophilic (*e.g.*, $-NH_2$, -OH, -SH, -NC, etc.) and electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, $-NH_3^+$), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof.

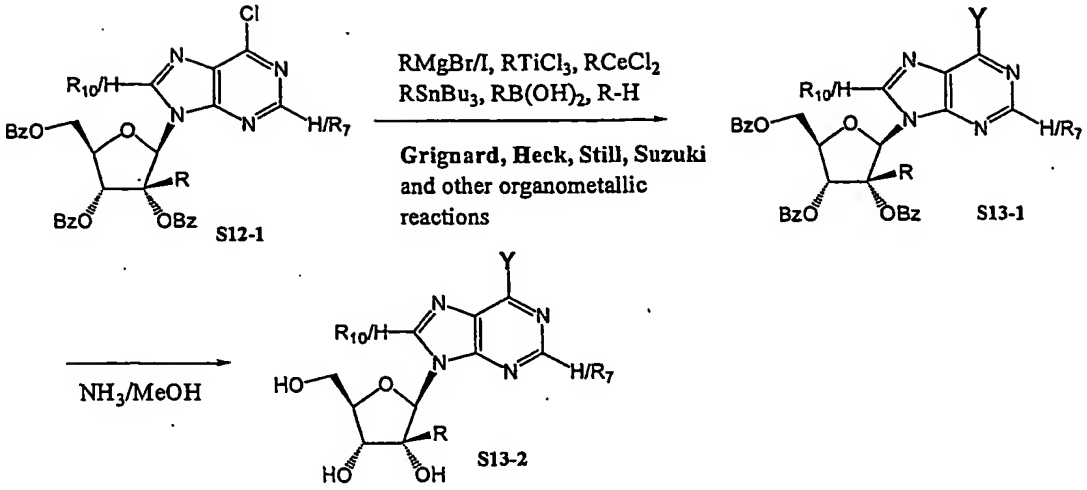
Contemplated Nucleosides

The present invention is generally directed to various heterocyclic nucleoside libraries and library compounds within these libraries, wherein contemplated compounds may be synthesized by medicinal and combinatorial approaches using solution and/or solid phase strategies. Furthermore, while most of the schemes below depict nucleosides and nucleoside analogs, it should be recognized that all of the contemplated nucleosides and nucleoside analogs may also be phosphorylated (preferably at the C5'-position) to the corresponding nucleotide or nucleotide analogs. Moreover, it should be appreciated that all prodrug forms and metabolites of the compounds according to the inventive subject matter presented herein are also contemplated.

6-C-Substituted Purine Nucleoside Libraries and Compounds

The inventors discovered that a 6-C-substituted purine nucleoside analog library and library compounds may be prepared by reacting an appropriate nucleoside having a leaving group in the 6-position with a strong nucleophilic reagent, which may or may not include coupling of the nucleoside to a solid phase.

More particularly, in one exemplary approach depicted in **Scheme 1**, a modified sugar is prepared by protecting the OH groups of the sugar, and subsequent selective deprotection and oxidation at the 2'-position via Dess-Martin reagent. The so prepared 2'-oxo-sugar is then reacted with a 2'-modifying reagent (*e.g.*, Grignard reagent) to yield the corresponding 2'-modified sugar that is then covalently coupled to a selected heterocyclic base with a leaving group in the 6-position. The resulting 2'-modified nucleoside analog is then reacted in a Grignard, Heck, Stille, or Suzuki reaction to replace the leaving group with a substituent, wherein the substituent is coupled to the 6-position via a carbon atom.



R_1 = H, CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl, cyclobutyl, $CH(CH_3)_2$, alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, CHF_2, CF_3, $CHCl_2$, CCl_3, CN, $C{\equiv}CH$ and others as described in different sections

R_7, R_{10} as described previously

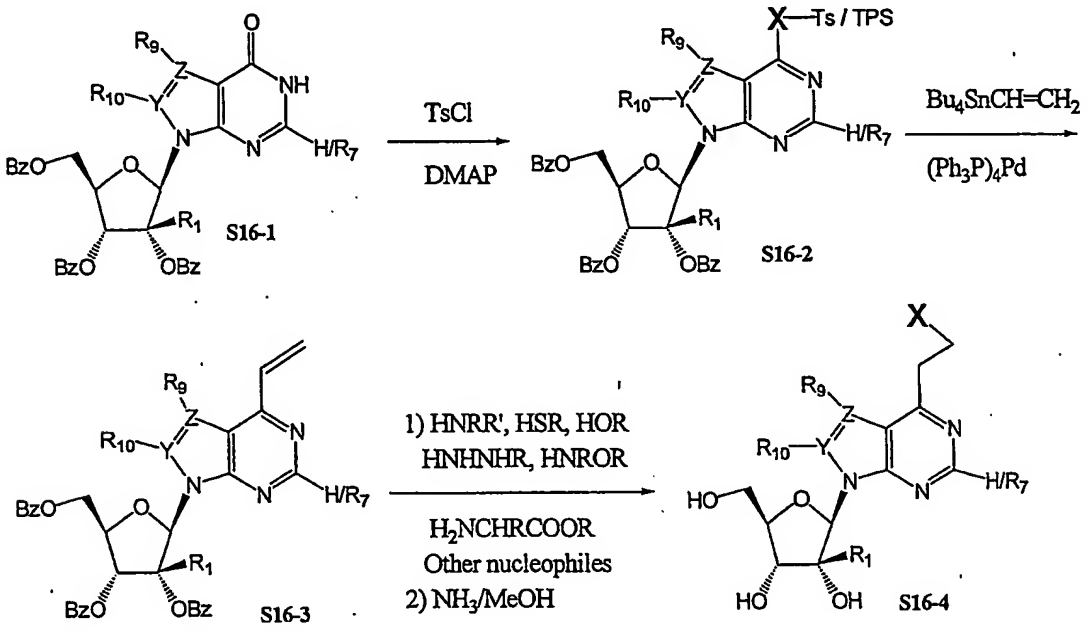
Y = alkyl, akenyl, alkynyl, aryl, substituted alkyl/alkenyl/alkynyl/aryl, heterocycles and other substituents in the building block lists

Scheme 1

It should be especially recognized that numerous 2'-modified sugar portions may be prepared according to the inventive subject matter, and that the chemical and biological nature of particular 2-modified sugars will typically depend on the modification reagent employed. Thus, all known Heck, Suzuki, Grignard, and Stille reagents are contemplated suitable for use herein, and a collection of exemplary suitable Heck, Suzuki, and Stille reagents is provided in the section entitled "Experiments and Data" below.

Similarly, the nature of the heterocyclic base may vary considerably, and all purine bases are considered suitable for use herein so long as such heterocyclic bases include a leaving group in the 6-position. Consequently, contemplated heterocyclic purine bases may be substituted in the 8-position and/or the 2-position with various substituents. Exemplary substituents for the 8-position include H, halogen, alkyl, alkenyl, alkynyl, or aryl (all of which may optionally be substituted) and exemplary substituents for 2-position may vary as well, but especially preferred substituents include H and NH_2. Furthermore, it should be recognized that all or almost all of such alternative heterocyclic bases are commercially available, or may be prepared by a person of ordinary skill in the art following well established protocols.

Alternatively, and especially where the newly introduced substituent in the 6-position has a reactive group (*e.g.*, double bond) that can be further modified, an exemplary synthetic route as shown in **Scheme 2** may be employed. Here, an ethenyl group is introduced into the 6-position of a nucleoside that was prepared following similar procedures as described above. The so introduced ethenyl group is then employed as an electrophilic group that is further modified with a nucleophilic group.



R_1 = H, CH_3, $CH=CH_2$, CH_2CH_3, $CH_2CH=CH_2$, -cyclopropyl, cyclobutyl, $CH(CH_3)_2$, alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, CHF_2, CF_3, $CHCl_2$, CCl_3, CN, $C\equiv CH$ and others as described in different sections

R_7, R_{10}, Z, Y are as described previously

X = NH_2, NHR, NRR, NHOH, NHOR, ONH_2, ONHR, $NHNH_2$, NHNHR, NRNHR, NHNRR, NRNRR, OR, SR, N_3, CN, NHCHRCOOR, amino acids (R are alkyl, akenyl, alkynyl, aryl, heterocycles and others) as well as other substituents in the building block lists

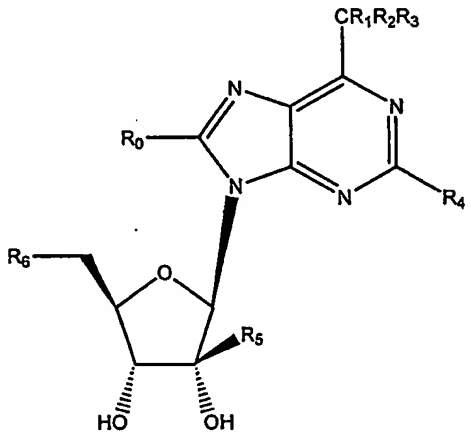
Scheme 2

With respect to the sugar, sugar modification, and the heterocyclic base, the same considerations as above apply. With further respect to the heterocyclic base, it is contemplated that the nature of suitable heterocyclic bases may vary considerably, and all purine bases are considered appropriate so long as such heterocyclic bases include an oxo-group in the 6-position. Consequently, contemplated heterocyclic purine bases may also be

substituted in the 8-position and/or the 2-position with various substituents. Exemplary substituents for the 8-position include H, halogen, alkyl, alkenyl, alkynyl, or aryl (all of which may optionally be substituted) and exemplary substituents for the 2-position may vary as well, but especially preferred substituents include H and NH_2. Furthermore, it should be recognized that all or almost all of such alternative heterocyclic bases are commercially available, or may be prepared by a person of ordinary skill in the art following well established protocols.

The inventors still further contemplate that modification of the introduced 6-substituent may provide a plurality of potential nucleoside analogs, and it should be recognized that the particular nature of the modification will typically depend on the type of reagent employed. However, it is generally preferred that the reagent for further modification is a nucleophilic reagent, and especially preferred nucleophilic reagents include a primary and/or secondary amine.

Therefore, contemplated library compounds will include those having a general structure according to Formula 1



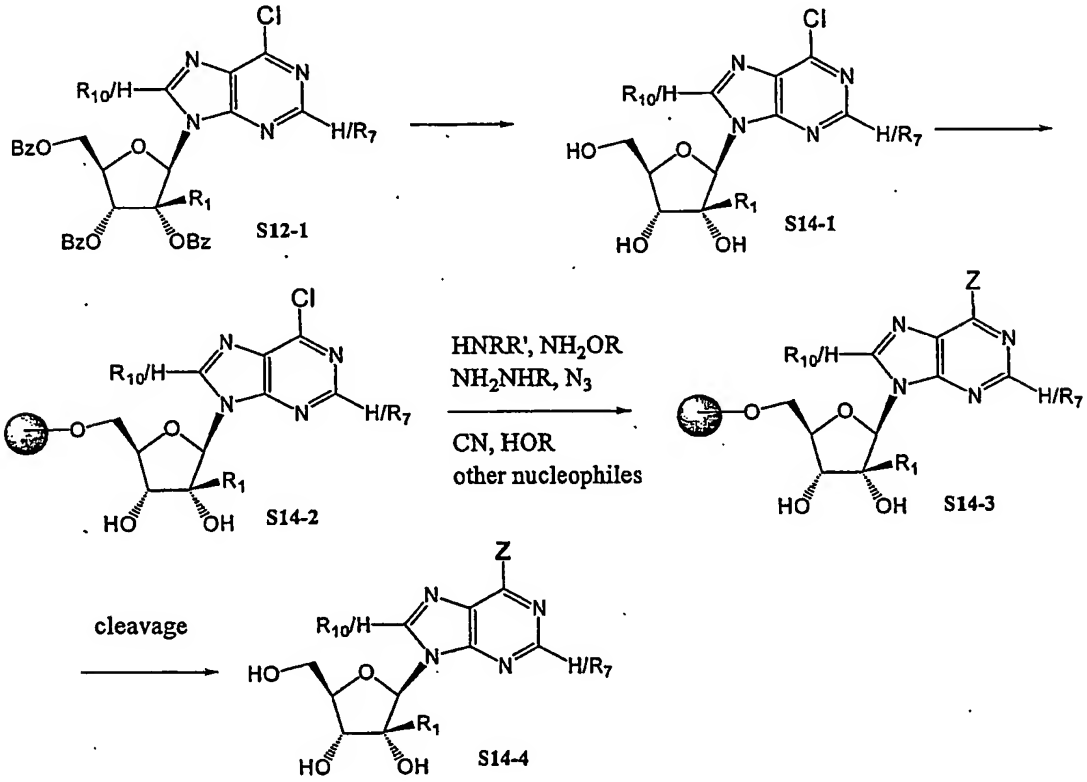
Formula 1

wherein the sugar is in D- or L-configuration; R_0 is H, halogen, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted); R_1, R_2, and R_3 are independently alkyl, alkenyl, alkynyl, aryl (all of which may be substituted), or H, and further preferred compounds include those in which R_1 and R_2 are H, and in which R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR', or alkyl-CN; R_4 is H or NH_2; R_5 is alkyl,

alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; R_6 is H, OH, phosphate, phosphonate, or boranophosphate; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

C_2'-Substituted-6,8-Modified Purine Nucleoside Libraries

In another contemplated aspect of the inventive subject matter, the inventors discovered that purine nucleoside analogs with 6-N-substituents may be prepared in a manner substantially similar to the methods described above, wherein the nucleophilic reagent to be introduced into the 6-position is a nucleophilic reagent other than a Heck/Still/Suzuki, and/or Grignard reagent. Such particularly preferred reagents include primary and secondary amines, alcohols, thiols, etc., and an exemplary synthetic route is depicted in **Schemes 3** and **Scheme 4** below.

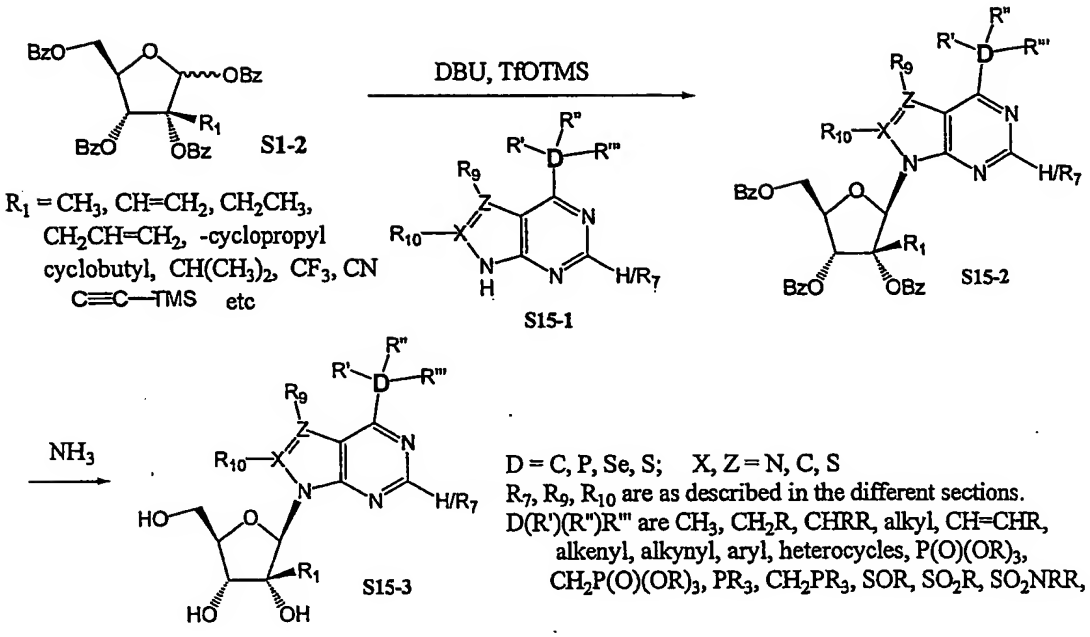


R_1 = H, CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl, cyclobutyl, $CH(CH_3)_2$, alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, CHF_2, CF_3, $CHCl_2$, CCl_3, CN, $C{\equiv}CH$ and others as described in different sections

R_7, R_{10} as described previously

X = NH_2, NHR, NRR, NHOH, NHOR, ONH_2, ONHR, $NHNH_2$, NHNHR, NRNHR, NHNRR, NRNRR, OR, SR, N_3, CN, etc (R are alkyl, akenyl, alkynyl, aryl, heterocycles and others) as well as other substituents in the building block lists

Scheme 3



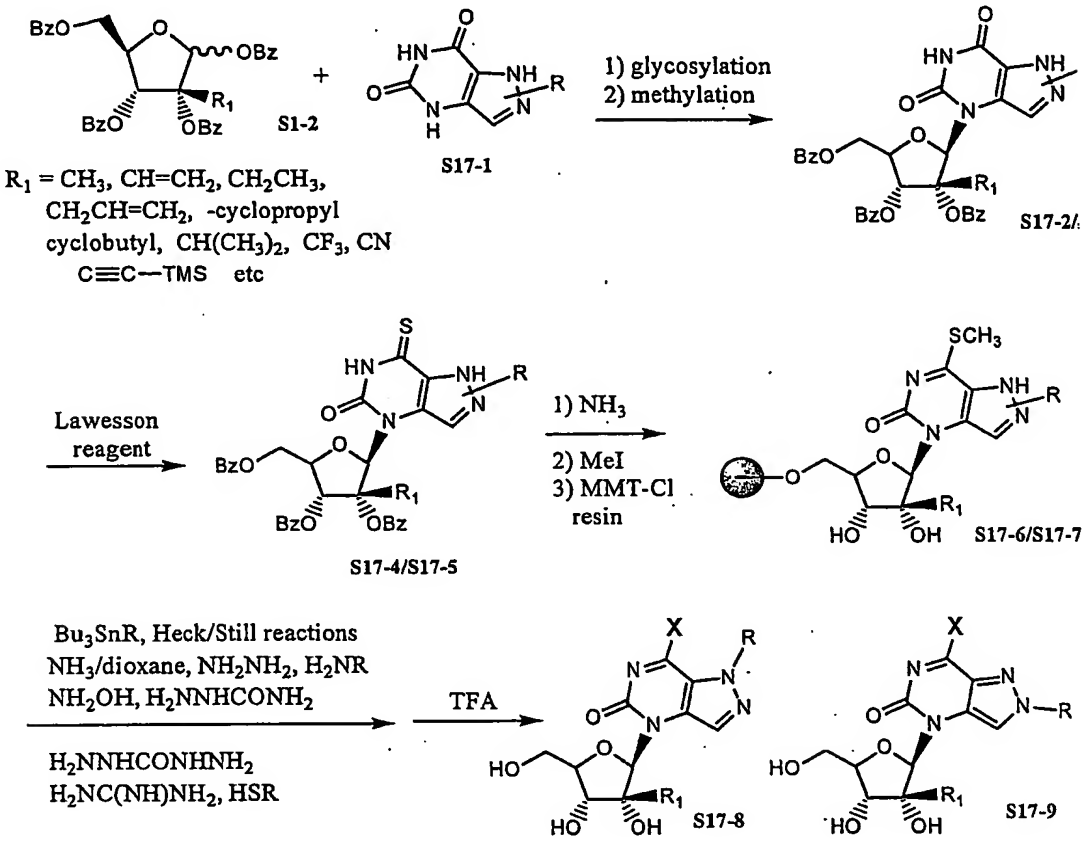
Scheme 4

Here, a suitably C_2'-substituted and protected sugar is first coupled to an optionally 7,8-modified purine heterocyclic base having a leaving group in the 6-position, which is then replaced by the nucleophilic reagent. Alternatively, a 2'-modified sugar is coupled to a 6-modified heterocyclic base to provide the desired nucleoside analog. With respect to the sugar, the sugar modification, and the heterocyclic base, the same considerations as described above apply.

C_2'-Substituted Modified Pyrazolopyrimidine Nucleoside Libraries

In a still further contemplated aspect of the inventive subject matter, the inventors discovered that C_2'-substituted modified pyrazolopyrimidine nucleoside libraries and compounds can be prepared. In an exemplary approach, as depicted in **Scheme 5** below, a heterocyclic base is coupled via the six-membered ring to a previously prepared 2'-modified sugar. In a further step or steps, one or both ketocarbonyl-groups are replaced with a thiocarbonyl group, wherein the thiocarbonyl group is further converted to a leaving group

that is subsequently replaced by a nucleophilic reagent to yield the desired compound(s). Of course it should be appreciated that one or more of the below depicted reactions may be performed in solution wherein the reagent or nucleoside analog is coupled to a solid phase.



R_1 = CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl cyclobutyl, $CH(CH_3)_2$, CF_3, CN C≡C—TMS etc

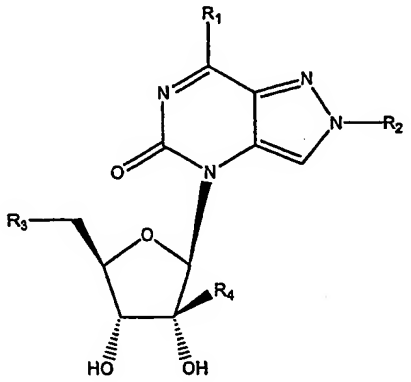
R_1 are the substituents described in different sections
R = alkyl, acyl, aryl, heterocycles
X = alkyl, aryl, alkenyl, alkynyl, NH_2, $NHNH_2$, NHR, NR_2, NHOH, NHOR, $NHNHCONH_2$, $NHNHCONHNH_2$, SR, CN, amidine, guanidine, hydroxyguanidine, mercaptoguanidine and other substituents in the building block lists

Scheme 5

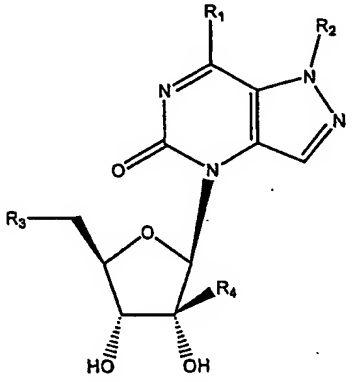
With respect to the sugar and the sugar modification, the same consideration as described above in the section entitled "6-C-Substituted Purine Nucleoside Libraries and Compounds" applies. It should further be recognized that various methods other than conversion of the ketocarbonyl group via a thiocarbonyl group to a leaving group may be employed, and all known alternative methods are contemplated suitable for use herein. For example, suitable conversions may employ reaction with TPSCl as described in Scheme 2 above.

It should still further be recognized that there are numerous reagents suitable for replacement of the leaving group in the heterocyclic base, and all known nucleophilic reagents are contemplated suitable for use herein. However, it is generally preferred that the nucleophilic reagent will include a primary and/or secondary amine, an alcohol, a thiol, a Heck-, Stille-, or Suzuki-reagent, or an organometallic reagent. Exemplary suitable nucleophilic reagents are provided in the section entitled "Experiments and Data" below.

Therefore, contemplated library compounds will include those having a general structure according to Formula 2A or Formula 2B



Formula 2A

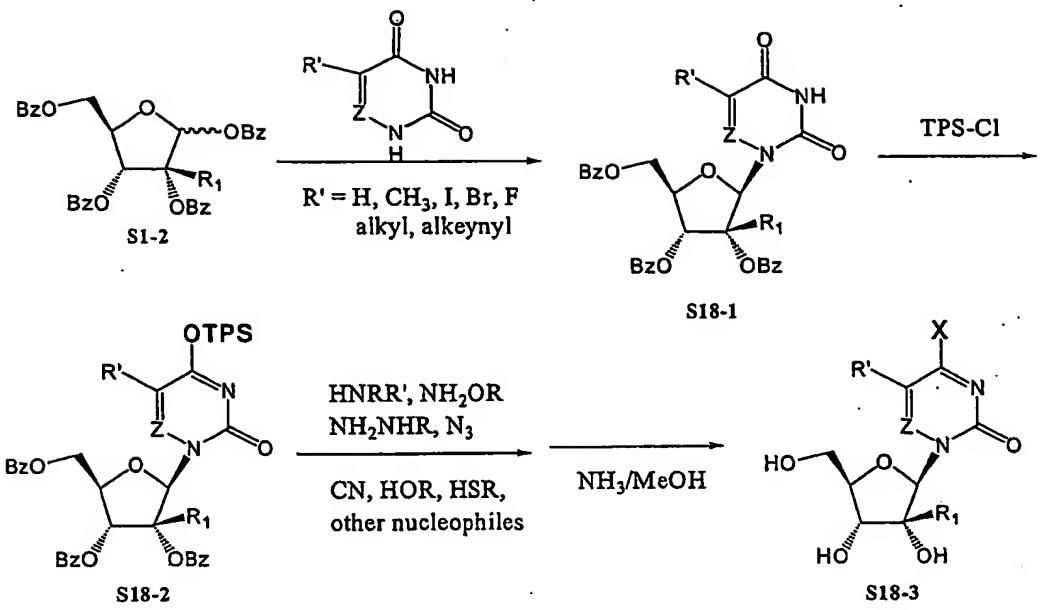


Formula 2B

wherein the sugar is in D- or L-configuration; R_1 is NR'R", ONR'R", NR'NR'R", SR', OR', or R'; R_2 is alkyl, acyl, or aryl; R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

C_2'-Substituted-Pyrimidine Nucleoside Analog Libraries

In yet further contemplated aspects of the inventive subject matter, the inventors discovered that C_2'-substituted-pyrimidine nucleoside analog libraries and compounds may be prepared in a protocol in which a modified pyrimidine heterocyclic base is coupled to a suitably protected C_2'-substituted sugar. An exemplary route for such libraries and compounds is depicted in **Scheme 6**. The so prepared nucleoside is then further modified to the desired compound(s).



Z = N, CH, CR

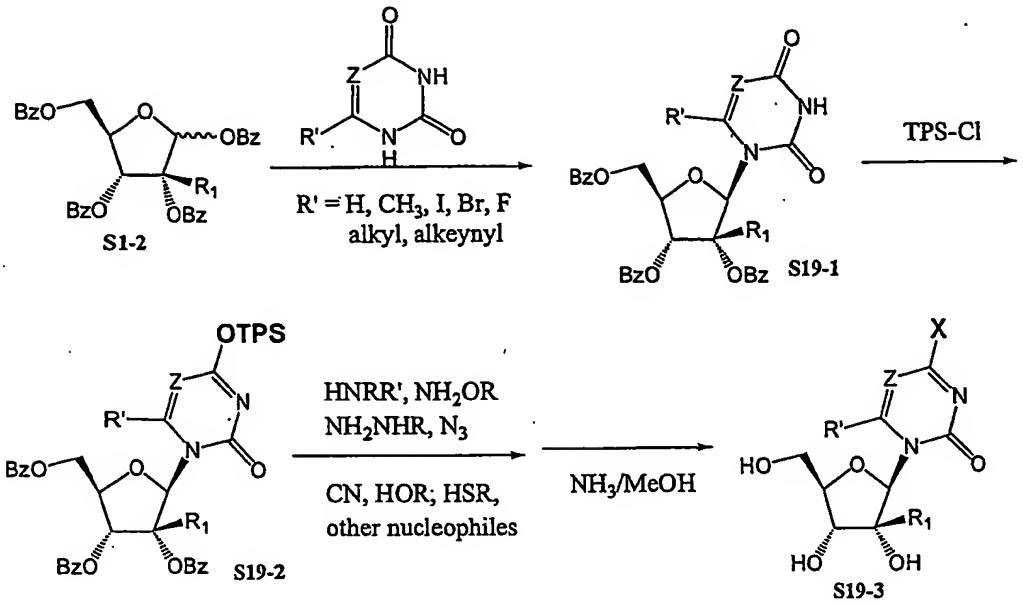
R' = aryl, heterocycles, alkenyl, alkynyl, substituted alkenyl/alkynyl and other substituents in the building lists

R_1 = H, CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl, cyclobutyl, $CH(CH_3)_2$, alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, CHF_2, CF_3, $CHCl_2$, CCl_3, CN, $C{\equiv}CH$ and others as described in different sections

X = NH_2, NHR, NRR, NHOH, NHOR, ONH_2, ONHR, $NHNH_2$, NHNHR, NRNHR, NHNRR, NRNRR, OR, SR, N_3, CN, NHCHRCOOR, amino acids (R are alkyl, akenyl, alkynyl, aryl, heterocycles and others) as well as other substituents in the building block lists

Scheme 6

Alternatively, where it is desired that the radicals Z and R1 of the heterocyclic base are switched in their position (as compared to the heterocyclic base of Scheme 6), contemplated nucleoside analog libraries and compounds may be prepared as depicted in **Scheme 7** below.



Z = N, CH, CR

R' = aryl, heterocycles, alkenyl, alkynyl, substituted alkenyl/alkynyl and other substituents in the building lists

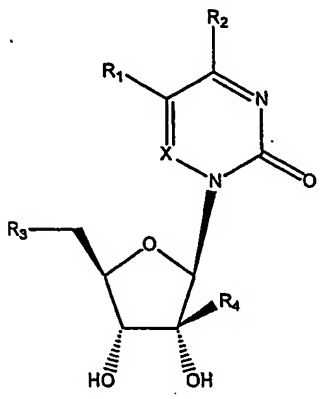
R_1 = H, CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl, cyclobutyl, $CH(CH_3)_2$, alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, CHF_2, CF_3, $CHCl_2$, CCl_3, CN, C≡CH and others as described in different sections

X = NH_2, NHR, NRR, NHOH, NHOR, ONH_2, ONHR, $NHNH_2$, NHNHR, NRNHR, NHNRR, NRNRR, OR, SR, N_3, CN, NHCHRCOOR, amino acids (R are alkyl, akenyl, alkynyl, aryl, heterocycles and others) as well as other substituents in the building block lists

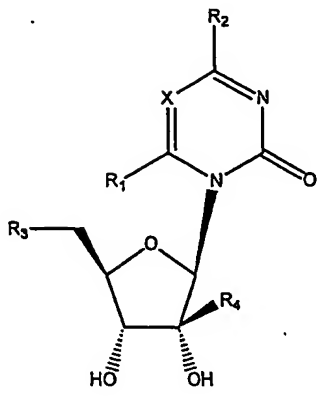
Scheme 7

With respect to the sugar, the sugar modification, and the coupling of the sugar to the heterocyclic base, the same considerations as discussed above apply. Furthermore, it should be appreciated that where the carbonyl oxygen can be converted into a leaving group using various methods well known in the art, suitable alternative methods to conversion with TPS-Cl include those as described in Scheme 5 above. Similarly, the nature of contemplated nucleophiles to replace the leaving group from the pyrimidine heterocyclic base may vary considerably, and all nucleophilic groups discussed above are considered suitable for use in conjunction with the teachings presented herein. Exemplary nucleophilic reagents therefore include various alcohols, thiols, organo-metallic reagents, and primary and secondary amines. Further particularly suitable exemplary nucleophilic reagents are listed in the section entitled "Experiments and Data" below.

Therefore, contemplated libraries and library compounds may include those having a structure according to **Formula 3A** or **Formula 3B**



Formula 3A

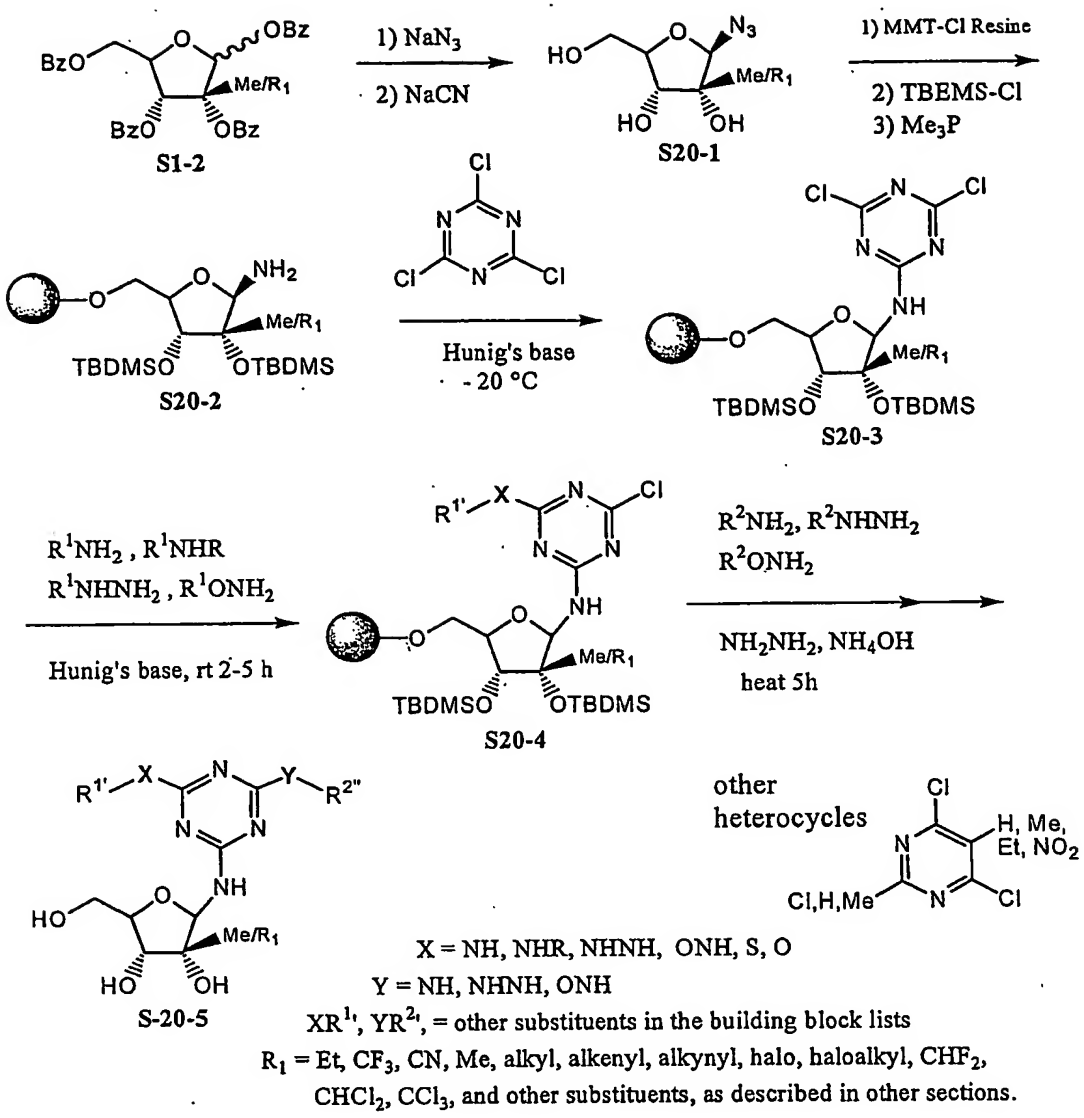


Formula 3B

wherein the sugar is in D- or L-configuration; X is N or CH; R_1 is H, halogen, alkyl, or alkenyl; R_2 is NR'R", ONR'R", NR'NR'R", SR', OR', or R'; R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

C_2'-Substituted-Exo-Triazine Nucleoside Libraries

In yet another contemplated aspect of the inventive subject matter, the inventors discovered that C_2'-substituted-triazine nucleoside libraries and compounds may be synthesized as shown in **Scheme 8** below, wherein a triazine heterocyclic base is coupled to the C_2'-substituted sugar via an atom other than carbon (here: amino group). In one exemplary route, trichlorotriazine is coupled to a 1'-amino sugar to form the corresponding nucleoside which is then further modified to the desired compound(s).



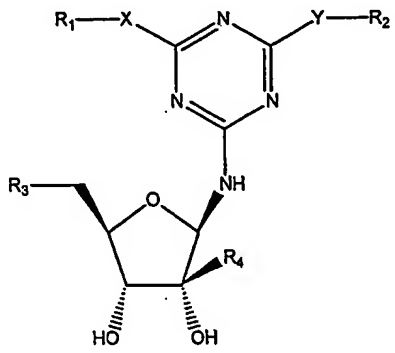
Scheme 8

Again, with respect to the sugar and the 2'-sugar modification, the same considerations as discussed above apply. Furthermore, it should be appreciated that while preparation of the amino sugar via an azido intermediate is generally preferred, commercially available 1'-amino sugars and their modifications are also considered suitable.

In a generally preferred aspect of the inventive subject matter, it is contemplated that the so prepared amino sugars may be coupled to a variety of heterocyclic bases, and it is generally contemplated that all heterocyclic bases are considered suitable so long as such bases (a) may be coupled via the NH_2 group of the sugar to the sugar, and (b) have at least one leaving group that can be replaced in a later step with a nucleophilic reagent. However, it

is particularly preferred that the heterocyclic base is a trichlorotriazine that is modified in a series of reactions to replace both remaining Cl- substituents with the respective nucleophilic reagents. Once more, with respect to the nucleophilic reagents that replace the leaving group(s) at the heterocyclic base, the same considerations as described above apply.

Therefore, contemplated libraries and library compounds may include those having a structure according to **Formula 4**



Formula 4

wherein X and Y are independently null, NR', O or S; R_1 and R_2 are independently NR'R", H, alkyl, alkenyl, alkynyl, or aryl (all of which may be further substituted); R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate; R_4 is alkyl, alkenyl, alkynyl, aryl (all of which may be further substituted), CN, or CF_3, and most preferably methyl; and R' and R" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted).

In particularly preferred aspects of the inventive subject matter, the sugar of above contemplated compounds is a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotides, contemplated 6,7-disubstituted-7-deazapurine nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred

modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

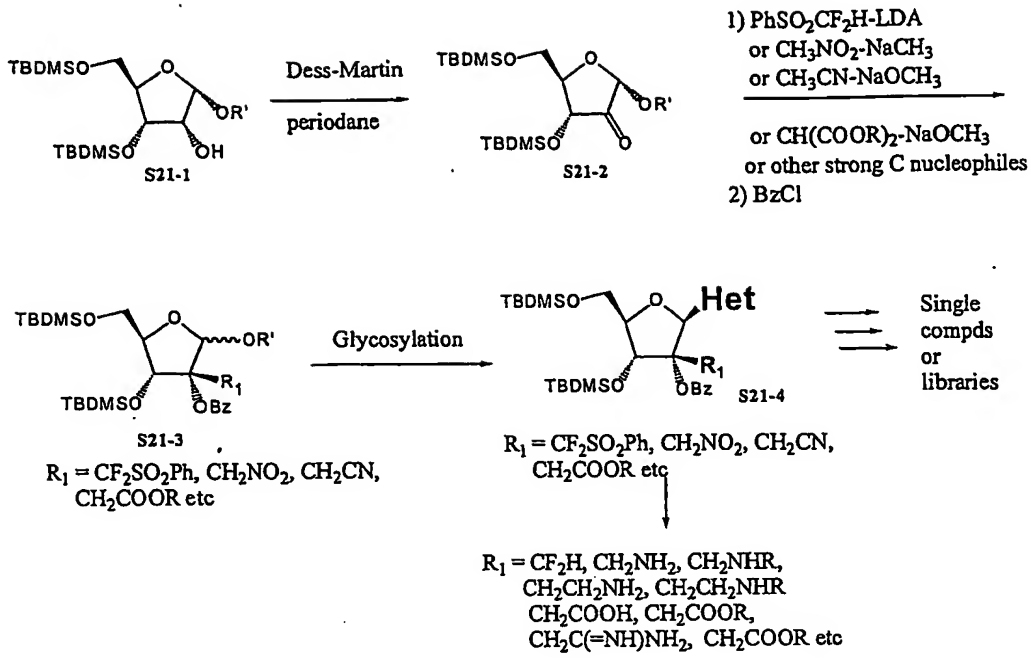
In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2'-beta (and especially a 2'-beta methyl or 2'-beta hydroxymethyl) modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improves the selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example suitable modifications on OH groups may include esterifications, and modifications on NH2 groups may include amidations.

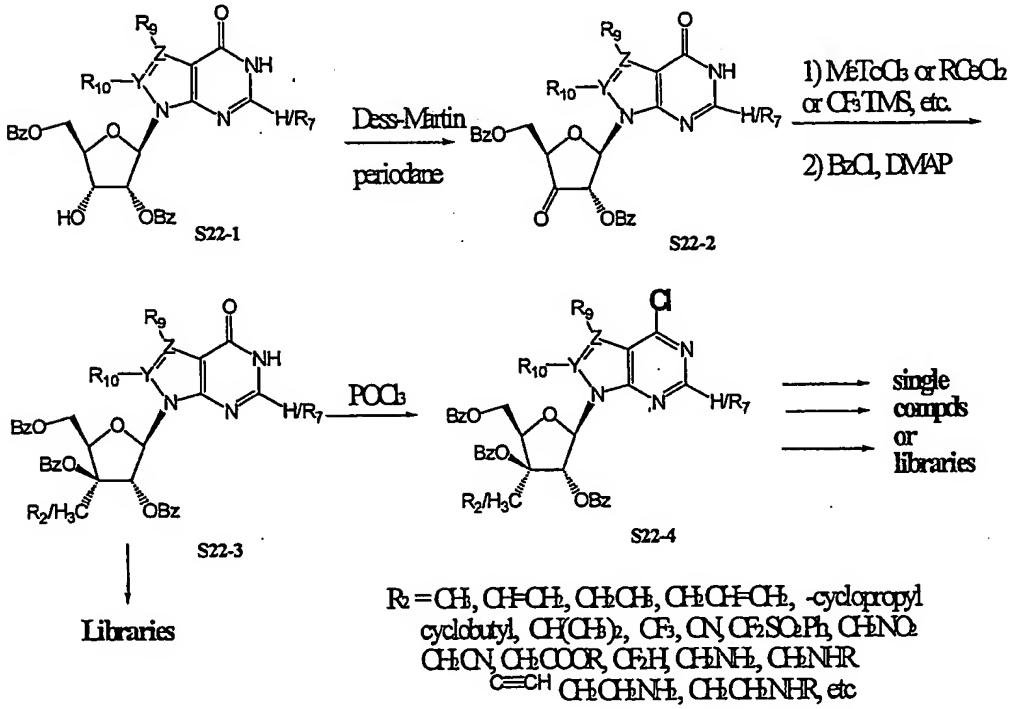
Modification Of The Sugar To Yield C_2'- And/Or C_3'-Substituted Sugars

It is generally contemplated that all known procedures and synthetic schemes for modification of a sugar to yield a C_2'- and/or C_3'-substituted sugar are suitable for use herein, and exemplary protocols may be found in "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan (Gordon & Breach Science Pub; ISBN: 3718659212), in U.S. Pat Nos. 4,880,782 and 3,817,982, in WO88/00050, or in EP199,451.

It should further be appreciated that the modification on the sugar portion of a nucleoside may be introduced when the sugar is covalently coupled to the heterocyclic base, or before coupling of the sugar to the heterocyclic base. Exemplary methods of introducing a substituents into the C_2'- or C_3'-position is depicted in **Schemes 9** and **10** below.

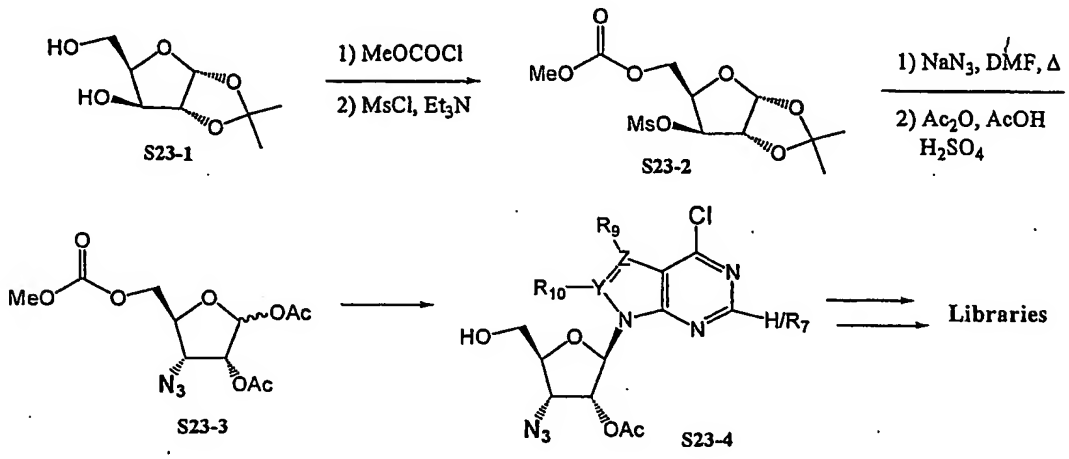


Scheme 9



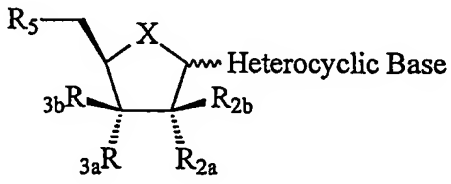
Scheme 10

Similarly, where azido sugars are desired, the azido group may be introduced via the corresponding azido salt in a reaction with a suitable protected sugar as shown in **Scheme 11** below.



Scheme 11

Thus, especially preferred alternative sugars for contemplated nucleosides include those having the general **Formula 5**



Formula 5

wherein Heterocyclic Base is any one of the heterocyclic bases contemplated herein; X is O, S, or CH_2, R_{2a} and R_{3a} are independently H, OH, SH, NH_2, NHR, OR, SR, CH_2OH, N_3, NH_2, COOH, halogen, or $P(O)(OR)_2$ with R being alkyl, acyl, or alkenyl (each of which may optionally be substituted); R_{2b} and R_{3b} are independently H, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2(CH_2)_{2\text{-}5}CH_3$, C_1-C_8 alkyl, alkenyl, or alkynyl (which may be linear, branched, or cyclic), C_5-C_{12}-aromatic or heterocyclic system, halogen (*i.e.*, F, Cl, Br, I), CF_3, CHF_2, CCl_3, $CHCl_2$, CH_2Cl, CH_2OH, CN, CH_2CN, CH_2NH_2, CH_2NHR, CH_2OR, CHO, CH_2COR, N_3, or NH_2, SH, NH_2, NHR, OR, SR, CH_2OH, N_3, NH_2, COOH, halogen, or $P(O)(OR)_2$ with

R being alkyl, acyl, or alkenyl (each of which may optionally be substituted), and wherein R_5 is OH, monophosphate, diphosphate, triphosphate, or analogs thereof (*e.g.*, phosphonate, boranophosphate, or thiophosphate).

Contemplated Prodrugs and Metabolites

It should still further be appreciated that the compounds according to the inventive subject matter also include prodrug forms, phosphorylated forms (most preferably at the C5'-atom) and/or metabolites. Particularly suitable prodrug forms of contemplated compounds may include a moiety that is covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, thereby replacing the OH group at the at least one of the C2'-atom, C3'-atom, and C5'-atom, wherein the moiety is preferentially cleaved from the compound in a target cell (*e.g.*, Hepatocyte) or a target organ (*e.g.*, liver). While not limiting to the inventive subject matter, it is preferred that cleavage of the prodrug into the active form of the drug is mediated (at least in part) by a cellular enzyme, particularly receptor, transporter, and cytochrome-associated enzyme systems (*e.g.*, CYP-system).

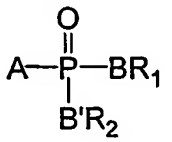
Especially contemplated prodrugs comprise a cyclic phosphate, cyclic phosphonate and/or a cyclic phosphoamidate, which are preferentially cleaved in a hepatocyte to produce the corresponding nucleotides. There are numerous such prodrugs known in the art, and all of those are considered suitable for use herein. However, especially contemplated prodrug forms are disclosed in WO 01/47935 (Novel Bisamidate Phosphonate Prodrugs), WO 01/18013 (Prodrugs For Liver Specific Drug Delivery), WO 00/52015 (Novel Phosphorus-Containing Prodrugs), and WO 99/45016 (Novel Prodrugs For Phosphorus-Containing Compounds), all of which are incorporated by reference herein. Consequently, especially suitable prodrug forms include those targeting a hepatocyte or the liver.

Still further particularly preferred prodrugs include those described by Renze et al. in Nucleosides Nucleotides Nucleic Acids 2001 Apr-Jul;20(4-7):931-4, by Balzarini et al. in Mol Pharmacol 2000 Nov;58(5):928-35, or in U.S. Pat. No. 6,312,662 to Erion et al., U.S. Pat. No. 6,271,212 to Chu et al., U.S. Pat. No. 6,207,648 to Chen et al., U.S. Pat. No. 6,166,089 and U.S. Pat. No. 6,077,837 to Kozak, U.S. Pat. No. 5,728,684 to Chen, and published U.S. Application with the number 20020052345 to Erion, all of which are incorporated by reference herein. Alternative contemplated prodrugs include those comprising a phosphate and/or phosphonate non-cyclic ester (SATE ester, pivaloyl ester,

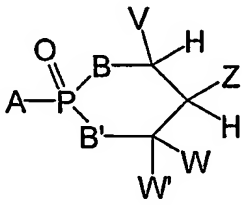
etc.), and an exemplary collection of suitable prodrugs is described in U.S. Pat. No. 6,339,154 to Shepard et al., U.S. Pat. No. 6,352,991 to Zemlicka et al., and U.S. Pat. No. 6,348,587 to Schinazi et al. Still further particularly contemplated prodrug forms are described in FASEB J. 2000 Sep;14(12):1784-92, Pharm. Res. 1999, Aug 16:8 1179-1185, and Antimicrob Agents Chemother 2000, Mar 44:3 477-483, all of which are incorporated by reference herein.

Thus, particularly preferred prodrug forms will comprise a moiety covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ. As used herein, the term "preferentially cleaved...in a target cell or target organ" means that cleavage occurs in a particular target cell or target organ at a rate that is at least 3 times, more typically at least 10 times, and most typically at least 50 times higher than in a non-target cell or non-target organ. The term "target cell" or "target organ" as used herein refers to a cell or organ that is infected with a virus, and especially includes a hepatocyte infected with an HCV virus. Cleavage may be mediated by enzymes (but also by non-enzymatic processes, *e.g.*, via reductive cleavage), and it is particularly preferred that enzymatic cleavage is mediated by a liver-specific enzyme system (*e.g.*, CYP system). Consequently, it should be appreciated that certain prodrug forms of contemplated compounds may be cleaved in a target cell and/or target organ to provide a nucleotide analog. Alternatively, prodrugs may also be converted to the corresponding nucleoside (*e.g.*, where the moiety does not include a phosphorus atom).

An exemplary preferred prodrug of contemplated compounds may therefore include a moiety according to **Formula M1** or **M2** (covalently coupled to the compound, typically to the C5'-atom, C2'-atom, and/or C3'-atom)



M1



M2

wherein A in M1 or M2 is O or CH_2 and replaces the 5'-OH group of the compound of Formulae 1 -5; B and B' are independently O or NH, and where B is NH then R_1 or R_2 is an amino acid that forms a peptide bond with the N atom of the NH; and R_1, R_2, V, W, and

W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH_2aryl. Especially preferred compounds according to Formula M2 are those in which A is O or CH_2, B and B' are independently O or NH, and in which Z, W, and W' are H and V is m-Chlorophenyl.

With respect to metabolites of contemplated compounds; it should be recognized that all metabolites that have a desirable therapeutic effect, and especially an antiviral effect are deemed suitable. Consequently, particularly suitable metabolites will generally include 5'-phosphates (*e.g.*, monophosphate, diphosphate, and/or triphosphate esters), which may or may not be generated by an enzyme (*e.g.*, kinase, oxidase). Further metabolites include those that are generated via enzymatic action on the heterocyclic base (*e.g.*, via deaminase, deamidase, or hydroxylase).

Use of Contemplated Compounds

It is generally contemplated that all libraries will comprise one or more nucleosides that have numerous biological activities, and especially contemplated biological activities include *in vitro* and *in vivo* inhibition of DNA and/or RNA polymerases, reverse transcriptases, and ligases. Therefore, contemplated nucleosides will exhibit particular usefulness as *in vitro* and/or *in vivo* antiviral agents, antineoplastic agents, and immunomodulatory agents.

Particularly contemplated antiviral activities include at least partial reduction of viral titers of respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, Hanta virus (hemorrhagic fever), human papilloma virus (HPV), yellow fever virus, and measles virus. The anti-HCV activity of the nucleosides and libraries were tested by Replicon and BVDV cell-line based assays. The HCV NS5B polymerase activity were tested for the mono-, di- and triphosphates of the nucleosides or 5'-methylenephospnonate derivatives. The compounds and libraries were tested for their replication of Hepatitis C virus RNA by cell-line based HCV Replicon assay as described in V. Lohmann, F. Korner, J.-O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, "Replication of a Subgenomic Hepatitis C virus RNAs in a Hepatoma Cell Line", Sciences, 1999, *285*, 110. Especially contemplated immunomodulatory activity

includes at least partial reduction of clinical symptoms and signs in arthritis, psoriasis, inflammatory bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma, but also modulation of some portion of a mammal's immune system, and especially modulation of cytokine profiles of Type 1 and Type 2. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2, suppression of Type 1 and stimulation of Type 2, or suppression of Type 2 and stimulation of Type 1.

Where contemplated nucleosides are administered in a pharmacological composition, it is contemplated that suitable nucleosides can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated nucleosides can be administered orally as pharmacologically acceptable salts, or intravenously in a physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated nucleosides may be modified to render them more soluble in water or other vehicle, which for example, may be easily accomplished with minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

In certain pharmaceutical dosage forms, prodrug forms of contemplated nucleosides may be formed for various purposes, including reduction of toxicity, increasing the organ or target cell specificity, etc. Among various prodrug forms, acylated (acetylated or other) derivatives, pyridine esters and various salt forms of the present compounds are preferred. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a target site within the host organism or patient. One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a targeted site within the host organism or patient to maximize the intended effect of the compound.

In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of various diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Experiments and Data

SYNTHESIS OF EXEMPLARY COMPOUNDS

Scheme 1

Synthesis of the Dess-Martin Reagent

1,1,1-Triacetoxy-1,1-Dihydro-1,2-Benziodoxol-3-(1H)-one: A 3L 3 neck RB flask was fitted with a mechanical stirrer, a heating mantle, a thermometer with adapter and a sodium hydroxide scrubber system. The vessel was charged with 100 g (0.403 mol) of 2-Iodobenzoic acid and 860 ml of 0.73 Molar sulfuric acid solution. The resultant white suspension was stirred and the pot temperature was increased to 55 °C at which point the vessel was charged with 87.3 g (0.523 mol) of potassium bromate, added in small portions over a 40 min time period. After the addition was completed the pot temperature of the thick orangish-amber suspension was increased to 70 °C, and the condition was maintained for a 3.5h time period. The reaction mixture was allowed to cool to ambient conditions. The reaction mixture was cooled to –1°C and maintained for a 0.5 h. The filter cake was washed with 1L of water, followed by 2 x 100 ml of ethyl alcohol, and then finally with 2 x 150 ml of diethyl ether. The cake was dried at high vacuum (~0.1mmHg)/ambient temperature for 24 h. 101.56 g of white powder was obtained in 90% yield.

A 1L 3 neck RB flask was fitted with a mechanical stirrer, a heating mantle, a thermometer with adapter, and a nitrogen inlet/outlet. The vessel was charged with 400 ml (4.24 mol) of acetic anhydride (4ml/g) and 0.5 g (0.00263 mol) of p-toluenesulfonic acid-monohydrate under nitrogen atmosphere and stirring. The reaction mixture was charged with

100 g (0.357 mol) of 1-hydroxy-1,2-benziodoxol-3-(1H)-one. The resulting pale yellow suspension (pot temp = 23 °C) was then heated to 80°C for 2h. The reaction mixture was allowed to cool to ambient temperature and then cooled to –2 °C. The white suspension was stirred at –2 °C for 0.5 h and filtered. The filter cake was washed with 5 x 50 ml of diethyl ether and then quickly transferred to an amber bottle under an argon atmosphere. The bottle was subsequently stored under refrigeration at < 5°C. 136.27 g of the desired product was obtained as a white solid in 90% yield. [This Dess-Martin reagent was synthesized in a large scale by a well modified and practical protocol based on the reported procedure: Cook, G. P.; Greenberg, M. M. J. Org. Chem. 1994, 59, 4704-4706].

Synthesis of 1',3',5'-Tri-*O*-benzoyl-D-ribofuranose was synthesized by a modified procedure based on the literature [Brodfuehrer, P. R.; Sapino, C., Jr.; Howell, H. G. J. Org. Chem. 1985, 50, 2598].

Synthesis of 1',3',5'-Tri-O-benzoyl-D-2-Ketoribofuranose: A 3L 3-necked RB flask was fitted with a mechanical stirrer, a thermometer with adapter, and a nitrogen inlet/outlet, to which was added 201 g (0.474 mol) of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin reagent) and 1000 mL (15.60 mol) of dichloromethane under nitrogen atmosphere. The reaction mixture was cooled to –1 °C, and 100 g (0.216 mol) of 1',3',5'-tri-O-benzoyl-D-ribofuranose was added. The resultant reaction mixture was stirred at room temperature for 24 hours and concentrated. The resultant residue was triturated with diethyl ether. The resultant ether triturate was filtered through a pad of Celite, and then treated with 1L of 1.0 M sodium thiosulfate solution. The organic phase was washed with sodium thiosulfate solution, and saturated sodium bicarbonate solution followed by brine. The organic phase was dried over magnesium sulfate and concentrated. The clear viscous pale yellow oily residue was subsequently dissolved in 2 L of dichloromethane. The solution was further treated with 500g of magnesium sulfate for 24 h and concentrated. The residue was further dried under high vacuum to provide 95.47 g (96%) of the desired product as a white foam. [Cook, G. P.; Greenberg, M. M. J. Org. Chem. 1994, 59, 4704-4706].

Synthesis of 1',2',3',5'-Tri-*O*-benzoyl-2-beta-*C*-methyl-D-ribofuranose : A 5L 3 neck RB flask was fitted with a mechanical stirrer, a thermometer with adapter, an additional funnel, a nitrogen inlet/outlet and a cooling bath. The vessel was charged with 2800 ml (26.74 mol) of diethyl ether (17 ml/g based on TiCl4) to which a continuous gentle stream of

nitrogen was passed over. The reaction mixture was stirred and cooled to –78 °C. 164.2g (0.868 mol) of titanium (IV) chloride was added drop wise over 1h. The resulting clear light yellow reaction mixture was treated with 289 ml (0.868 mol) of 3 Molar methyl magnesium bromide in diethyl ether drop wise. The reaction mixture was allowed to slowly warm to a pot temperature of –30 °C at which point 100 g (0.217 mol) of 1,3,5-tri-*O*-benzoyl-alpha-D-2-keto-ribofuranose in 200 ml of diethyl ether (2ml/g) was added drop wise. The reaction mixture was allowed to stir at –30 °C for a 4 h. The organic phase was separated, and the aqueous phase was extracted with 3 x 2000 ml of diethyl ether. The combined organic phase was washed with water and then dried over magnesium sulfate. The organic solution was concentrated, and the residue was subsequently dried at high vacuum (~0.1mmHg)/ambient temperature for a 24 h to provide 100.3 g (97%) of intermediate compounds as a clear viscous oil, which were then used directly for the next step.

A 2L 3 neck RB flask was fitted with a mechanical stirrer, a thermometer with adapter, an addition funnel, and a nitrogen inlet/outlet to which were added 6.63 g (0.0543 mol) of 4-dimethlyaminopyridine and 500 ml (7.80 mol) of dichloromethane under nitrogen atmosphere. 85 ml (0.613 mol) of triethylamine was added followed by the addition of 12.6 ml (0.1086 mol) of benzoyl chloride drop wise. 25.87 g (0.0543 mol) of sugar intermediates 5 and 6 obtained above in 125ml of dichloromethane (5ml/g) was added drop wise. The resulting clear light amber reaction mixture was allowed to stir at ambient conditions for 3h to complete the reaction (TLC analysis on silica gel, 4:1 Hex/EtOAc). The reaction mixture was diluted with 2.5L of diethyl ether, and the clear pale amber solution was partitioned with a 750ml portion of 1 Molar HCl solution in an extraction vessel. The organic phase was separated and washed with 2 x 500 ml of 1 Molar HCl solution, followed by a 500 ml of water and 2 x 500ml portions of saturated sodium bicarbonate solution. The organic solution was dried over sodium sulfate and concentrated. The remaining residue was subsequently pumped at high vacuum/ambient temperature for a 14 h. The crude product was flashed through a 740 g plug of silica gel (20:1) packed and loaded with 9:1 hexane/ethyl acetate and eluted with a gradient from 9:1 to 4:1 hexane/ethyl acetate. The desired fractions were combined and evaporated on a rotary evaporator at 26mmHg/bath temperature 35°C and the remaining residue was pumped at high vacuum (~0.1mmHg)/ambient temperature for a 14 h to provide 17.03 g (54%) of the desired product 7 as a pale yellow solid. 1H NMR (CDCl3) d 1.97 (s, 3H), 4.56 (dd, 1H, J = 4.8, 12.0 Hz), 4.68 (dd, 1H, J = 4.8, 12.0 Hz), 4.80 (m, 1H),

5.98 (d, 1H, J = 8.0 Hz), 7.02 – 8.15 (m, 21 H). [Wolfe, M. S.; Harry-O'kuru, R. E. Tetrahedron Lett. 1995, 36, 7611-7614; Harry-'Okuru, R. E.; Smith, J. M.; Wolfe, M. S. J. Org. Chem. 1997, 62, 1754-1759].

6-Chloro-9*H*-(2'-β-*C*-methyl-2',3',5'-tri-*O*-benzoyl-*β*-D-ribofuranosyl)purine (12-1) was prepared based on the literature procedure with modification (P. Franchetti, L. Cappellacci, S. Marchetti, L. Trincavelli, C. Martini, M. R. Mazzoni, A. Lucacchini, M. Grifantrini, *J. Med. Chem.* **1998**, *41*, 1708-1715). To a stirred mixture of 6-chloropurine (1.82 g, 11.08 mmol) and 2'-β-C-methyl-1,2,3,5-tetra-*O*-benzoyl-D-ribose (6.44 g, 35.46 mmol) in anhydrous CH_3CN (200 ml) under an Argon atmosphere was added 1',8-diazabicyclo[5.4.0]undec-7-ene (5.39 g, 35.46 mmol) at room temperature. The stirred mixture was cooled to 0 °C under Argon atmosphere. Me_3SiOTf (10.49 g, 47.23 mmol) was added to the reaction mixture slowly during a 15 minute period at 0 °C. The reaction mixture was then warmed to room temperature during a 30 minute period. The resulting reaction mixture was heated at 60 °C for 4 h and concentrated to dryness. The residue was partitioned between ethyl acetate and saturated $NaHCO_3$ (300/200 ml). The organic phase was separated, and the aqueous phase was extracted in ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The resultant residue was purified by flash chromatography on a silica gel column using hexane → EtOAc as the eluent. The pure fractions were collected and concentrated to dryness to provide 6.60 g (95%) of the titled compound. ^1H NMR ($CDCl_3$) δ 1.61 (s, 3 H), 4.77 (m, 1 H), 4.93 (m, 2 H), 6.21 (d, 1 H), 6.82 (s, 1 H), 7.30–7.62 (m, 9 H), 7.94–8.12 (m, 6 H), 8.30 (s, 1 H), 8.79 (s, 1 H).

Modification of the compound 12-1 to yield compounds **(13-1)** was performed under conditions substantially similar to those described in J.W. Labadie, D Tueting, and J.K. Stille. *J. Org. Chem.* 48,4634 (1983), or in A.M. Echavarren and J.K. Stille. *J. Am. Chem. Soc.* 110, 1557 (1988)) for Stille reactions, or those described in R.F. Heck. *Org. React.* N.Y. 27, 345 (1982), or J.E. Plevyak and R.F. Heck. *J. Org. Chem.* 43, 2454 (1978) for Heck reaction, or those described in N. Miyaura, T. Yanagi, and A. Suzuki. *Synth. Commun.* 11, 513 (1981); A. Suzuki. *Pure Appl. Chem.* 57, 1749 (1985), or M. Sato, N. Miyaura, and A. Suzuki. *Chem. Lett.* 1405 (1989) for Suzuki reaction. Similarly, where a Grignard reaction was employed to yield compounds 13-1, protocols substantially similar to those described in Grignard V.

Compt. Rend., 1900, 130, 1322, or Shirley, D.A. *Org. React.*, 1954, 8, 28-58 were used. Subsequent deprotection using methanolic ammonia was performed using a general deprotection protocol well known to a person of ordinary skill in the art to provide library and library compounds (**13-3**).

Scheme 2

Toluene-4-sulfonyl chloride (3.8 g, 20 mmol) was added to a suspension of **S16-1** (Y-R_{10} is C-H, and Z-R_9 is N-null) (10 mmol), triethylamine (2.87 ml, 20 mmol), and DMAP (244 mg, 2 mmol) in 150 ml of anhydrous dichloromethane at 0 °C under argon. The reaction mixture was stirred at room temperature overnight. A clear brown solution was obtained. The reaction mixture was diluted with dichloromethane and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulfate, concentrated to a small volume, and then added to 1,000 ml of hexanes with vigorous stirring at room temperature. The resulting precipitate was filtered and washed with hexanes to give product **S16-2** as a white solid.

A solution of **S16-2** (1 mmol), lithium chloride (85 mg, 2 mmol), and of $Pd(PPh_3)_4$ (231 mg, 0.2 mmol) in 15 ml of anhydrous dioxane was stirred under argon at room temperature for 10 min. Tributyl(vinyl)tin (1.46 ml, 5 mmol) was added and the mixture was heated under reflux for 4 hours. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography on a silica gel column using chloroform-methanol (50:1) as an eluent to give pure product **S16-3** as yellow foam.

To a solution of **S16-3** (1 equiv) in chloroform-methanol (50:1) or ethanol was added amino acid ester, amines, thiophenols, mercaptans and other nucleophiles (1 equiv) at room temperature or elevated temperature. The resulting mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the residue was purified by flash chromatography on a silica gel column using chloroform-methanol (50:1) as an eluent to give the corresponding 6-substituted ethyl purine nucleoside derivatives **S16-4**.

Schemes 3 and 4

Compounds and libraries **S14-4** And **S15-3** were prepared following substantially similar protocols as described for Schemes 1 and 2 above.

Scheme 5

5,7-Dihydroxy-1(2)-methylpyrazolo[4,3-d]pyrimidine **S17-1** was synthesized by heating 4-amino-1(2)-methylpyrazole-3-carboxyamide (11.61 g, 82.85 mmole) and urea (12 g) at 120° C for 20 minutes. After cooling, the crude product was dissolved in 2N NaOH (200 ml) and acidified with AcOH to pH 3-4. The precipitated solid was filtered, washed with water and dried at high vacuo over solid NaOH to give 11.01 g (80%) of light brown solid.

4-(2,3,5-Tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1-methylpyrazolo[4,3-d]pyrimidine-5,7(6*H*)-dione S17-2 and 4-(2,3,5-Tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2-methylpyrazolo[4,3-d]pyrimidine-5,7(6*H*)-dione **S17-3**. A mixture of **S17-1** (11.01 g, 66.28 mmole), ammonium sulfate (0.2 g), dry pyridine (50 ml) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 200 ml) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was co-evaporated with dry xylene (100 ml) and mixed with dry acetonitrile (200 ml). Ribose derivatives **S1-2** (70.00 mmole) were added and cooled to 0° C under argon atmosphere. To this cold stirred mixture was added trimethylsilyl trifluoromethanesulfonate (TMS triflate, 15.00 ml) dropwise during 30 minutes period. After the addition, the solution was gradually warmed to room temperature and stirred overnight. Methanol (30 ml) was added, stirred for 15 minutes and evaporated to dryness. The residue was dissolved in ethyl acetate (500 ml), and washed successively with saturated $NaHCO_3$ solution (3x200 ml), water (300 ml) and brine (200 ml). The organic extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ EtOAc as the eluent. Two products were isolated. The fast moving product (33%) was assigned as compound **S17-2** (1-methyl). The slow moving product (50%) was assigned as compound **S17-3** by 2D NMR.

A mixture of compound **S17-2** (30.16 mmole) and Lawesson's reagent (24.40 g, 60.33 mmole) in dry pyridine (150 ml) was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was treated with sat. $NaHCO_3$ solution (300 ml) and extracted with EtOAc (300 ml). The organic extract was washed with brine (150 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ EtOAc as the eluent to give 15.48 g (82%) of S17-4 as yellow foam. **S17-5** was synthesized by the same approach.

Compound **S17-4** (23.96 mmole) was allowed to stir with methanolic ammonia (250 ml) in a steel bomb at room temperature for 2 days. The steel vessel was cooled, opened and the solution was evaporated to dryness. The residue was crystallized from methanol/ethyl acetate to give 6.02 g (80%) of light brownish solid. A solution of the resultant compound (17.52 mmole) in dry DMF (100 ml) was treated with N,N-diisopropylethylamine (2.46 g, 19.00 mmole) at room temperature. After 30 minutes, methyl iodide (5 ml) was added and the stirring continued for 12 h. The reaction mixture was filtered, and the solid was washed with dry DMF (50 ml). The combined filtrate was evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ MeOH as the eluent to give 4.71 g (82%) of yellow solid. A suspension of this compound (13.72 mmole) and psMMTCl-resin (5.56 g) in dry pyridine (40 ml) was shacked at room temperature for 3 days. The reaction mixture was quenched with methanol (20 ml) and shacked for an additional 30 minutes. The resin was filtered, washed with dry DMF (2x20 ml), MeOH (2x20 ml), and CH_2Cl_2 (2x20 ml). The resin was dried in vacuo at 45° C overnight to give resin **S17-6**. Resin **S17-7** was synthesized by the same approach.

A suspension of resin **S17-6** or **S17-7** (100 mg) and various amines and other nucleophilic building blocks (see building block lists) (2 equiv.) were heated at 60° C for 12 and filtered. The resins were washed with CH_2Cl_2 (2x10 ml), MeOH (2x10 ml), DMF (2x10 ml) and CH_2Cl_2 (2x10 ml). These resins were shaken with 5% TFA (2 ml) at room temperature for 1 h and filtered. The filtrate was evaporated to dryness. The residues were co-evaporated with dry toluene (2x5 ml) to give 15-25 mg of libraries **S17-8** or **S17-9** as amorphous solid single compounds.

Scheme 6

Compound **S18-1** was prepared by the similar procedure as reported (P. Franchetti, L. Cappellacci, S. Marchetti, L. Trincavelli, C. Martini, M. R. Mazzoni, A. Lucacchini, M. Grifantrini, J. Med. Chem. 1998, 41, 1708-1715). A solution of S18-1 (1 equiv, DMAP (100 mg), dichloromethane (30 ml) and triethylamine (6.8 ml) was stirred at room temperature for 30 minutes. 2,4,6-tris(isopropyl)benzenesulfonyl chloride (TIP-Cl, 4.24 g, 2 equiv) were added. The resultant mixture was stirred at room temperature for 24 hours. 2 ml of methanol were added to consume the excess amount of TIP-Cl, shaken and filtered. The solution was concentrated and purified by chromatography on a silica gel column providing compound

S18-2 as white foam. This compound was reacted in parallel with various amines and other nucleophiles (see building block lists) at room temperature or elevated temperature. The resulted compounds were treated with ammonia to provide the final single compounds **S18-3**. Compounds **S19-3** are synthesized by the similar approach.

Scheme 7

Scheme 7 followed the protocol of Scheme 6 with the exception that the positions of the radicals Z and R_1 in the heterocyclic base were switched (relative to the heterocyclic base shown in Scheme 6). Otherwise, the same conditions and procedures were employed.

Scheme 8

To a solution of ribofuranose-1-acetate derivatives **S1-2** (9.91 mmol) in 50 ml of dimethylformamide was added 0.97 g of sodium azide (14.87 mmol). The mixture was stirred at 115 °C for 16 hours under argon and then evaporated. The residue was extracted by chloroform and dried over sodium sulfate. The resultant compound was treated with NaCN to give compound **S20-1**.

To a suspension of polystyrene monomethoxytrityl chloride resin (1 g, 1.73 mmol/g) in pyridine (4 ml), a solution of β-D-ribofuranosyl-1-azide derivatives **S20-1** (3.46 mmol) in pyridine (4 ml) was added which was followed by the addition of 4-dimethylaminopyridine (0.122 g, 1 mmol). The reaction mixture was shaken well for 48 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (3x25 ml) and a mixture (8.5:1:0.5) of MeOH, CH_2Cl_2 and diisopropylethylamine. The product resin was then dried over KOH under vacuum for 16 h. The loading efficiency was 85% (1.46 mmol alcohol loaded). To a suspension of this resin in DMF were added excess amounts of TBDMS-Cl (1.29 g, 8.65 mmol) and imidazole (1.17 g, 17.3 mmol). The reaction mixture was shaken for 16 h at room temperature. The resin was filtered and washed with DMF (3x10 ml), MeOH (3x10 ml) and CH_2Cl_2 (3x10 ml). The resin was then dried over KOH under vacuum for 16 h. To a suspension of the resultant resin (1.1 g) in a mixture (7.4 ml) of THF and water (9:1), a solution (1 M) of PMe_3 in THF (2.6 ml) was added and shaken well at room temperature for 6 h. The resin was filtered and then washed with THF and water mixture (1:1, 3x10 ml), MeOH (3x10 ml), CH_2Cl_2 (3x10 ml). The resin **S20-2** was then dried over KOH under vacuum for 16 h.

The resin **S20-2** (1 g) was suspended in a solution of diisopropylethylamine in CH_2Cl_2 (5 ml, 20%v/v) and cooled to 0-5 °C (ice-cold water). It was then treated with a CH_2Cl_2 solution (5 ml, 1 M) of cyanuric chloride. The resin suspension was shaken at room temperature for 1 h and filtered using a sintered funnel. The resin S20-3 was washed with CH_2Cl_2 (3x25 ml) and dried over KOH under vacuum for 16 h.

To a suspension of resins **S20-3** (0.05 g) in an NMP solution of DIPEA (0.75 ml, 20%v/v), an NMP solution (0.75 ml, 1M) of amines (see building block lists) was added and the reaction mixture was shaken well at room temperature for 2 h. The resin was then washed with NMP (3x10 ml), MeOH (3x10 ml) and CH_2Cl_2 (3x10 ml). The resins S20-4 were then dried over KOH under vacuum for 16 h. To a suspension of resins S20-4 (0.05 g) in an NMP solution of DIPEA (0.75 ml, 20%v/v) was added an NMP solution (0.75 ml, 1M) of amines (see building block lists) and the reaction mixture was shaken well at 80 °C for 6 h. The resins were then washed with NMP (3x10 ml) and CH_2Cl_2 (3x10 ml) and then dried over KOH under vacuum for 16 h. A suspension of above resins (0.05 g) in THF solution (1.5 ml, 1 M) of TBAF was shaken well at room temperature for 16 h. The resins were filtered and treated with DMF-acetic acid mixture (1.5 ml, 9:1) for 60 seconds and filtered. The resins were washed with DMF-water mixture (9:1, 3x10 ml), MeOH (3x10 ml) and CH_2Cl_2 (3x20 ml) and dried over KOH under vacuum for 16 h. A suspension of above resins (0.05 g) in CH_2Cl_2 solution (1.5 ml, 1.5%) of TFA were shaken well at room temperature for 60 seconds and filtered. The resins were further washed with MeOH (2x1 ml) and the combined filtrates were evaporated to dryness to give libraries **S20-5**. These libraries were synthesized by the parallel 96-well synthesizer. Twelve plates (96 X 12) were synthesized having 95-98% over 60% purity detected by LC-MS spectrometry.

Exemplary Amino Building blocks (R-NH_2 or RNHR) used for the libraries

1-(Benzyl)benzylamine, 2-phenyl-n-propylamine, m-trifluorobenzylamine, 2,2-diphenylethylamine, cyclobutylamine, methylcyclohexylamine, 2-methylpropylamine, allylcyclopentanylamine, N-methyl-4-piperidinylmethylamine, 4-hydroxypiperidine, 3-hydroxypiperidine, 1-benzylpiperazine, p-methoxybenzylamine, N,N-

bis(isopropyl)aminoethylamine, 2-ethylhexylamine, 5-methyl-2-furanosylmethylamine, N,N-dimethylaminopropylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methylbutylamine, o-ethoxybenzylamine, 3-(2-methyl-N-piperidinylpropylamine, 1-(2-aminoethyl)pyrrolidine, 2-morpholinylethylamine, N4-hydroxyethylpiperazine, N-methylethylenediamine, 3-morpholinylpropylamine, pyridinyl-2-ethylamine, butylamine, hexylamine, methylamine, 2-hydroxyethylamine, N,N-dimethylethylenediamine, 3-methoxypropylamine, 2-methoxylethylamine, ethylamine, 2-isopropylamine, methylethylamine, 2-methylthioethylamine, di-n-butylamine, dimethylamine, allylamine, cyclopantylamine, 2-(N-methyl-pyrrolidin-2-yl)ethylamine, tetrahydrofuranosyl-2-methylamine, piperidine, N-benzyl-4-aminopiperidine, aminomethylcyclopropane, cyclopropylamine, 3-methylpiperizine, 4-piperidin-1-ylpiperidine, cyclohexylamine, piperazine, 4-pyridin-2-ylpiperazine, 1-methylpiperazine, N-(2-methoxyphenyl)piperazine, N-pyrimidin-2-ylpiperazine, cycloheptylamine, p-trifluorobenzylamine, benzylamine, 3-imidazol-1-ylpropylamine, exo-2-aminonorborane, N-phenylethylenediamine, 1-methylbenzylamine, 3,4-(1,3-dioxolanyl)benzylamine, pyridin-2-ylmethylamine, pyridin-3-ylmethylamine, pyridin-4-ylmethylamine, thiophen-2-ylmethylamine, 3,3-dimethylbutylamine, o-methoxybenzylamine, 1-(3-aminopropyl)pyrrolidin-2-one, N-methylethylenediamine, m-methylbenzylamine, 3-methylbutylamine, 2-methylbutylamine, heptylamine, 3-butoxypropyamine, 3-isopropoxypropylamine, 2-morpholin-4-ylpropylamine, N1,N1-diethylethylenediamime, 2-ethylthioethylamine, 4-(2-aminoethyl)phenol, furfurylamine, 4-aminomethylpiperidine, 2-(2-aminoethyl)pyridine, 2-phenoxyethylamine, 2-aminoethylthiophene, p-methoxybenzylamine, 2-(N,N-dimethylamino)ethylamine, 1-amino-2-propanol, 5-methylfurfurylamine, 3-(dimethylamino)propylamine, o-methoxybenzylamine, 1-(3-aminopropyl)-2-pipecoline, hydrazine, 4-hydroxypiperidine, ethylenediamine, 1,4-diaminobutane, N-methylpropylamine, trans-1,4-diaminocyclohexane, 2,2,2-trifluoroethylamine, 3-chloropropylamine, 3-ethoxypropylamine, aminoacetaldehyde dimethyl acetal, 3-amino-1,2-propanediol, 1,3-diamino-2-hydroxypropane, 1-aminopyrrolidine, 2-(2-aminoethyl)-1-methylpyrrolidine, 3-methylpiperidine, 2-piperidine methanol, 3-piperidine methanol, 1-aminohomopiperidine, homopiperazine, 4-aminomorpholine, 3-bromobenzylamine, piperonylamine, 1,2,3,4-tetrahydroisoquinoline, L-proline methyl ester, 1-(2-pyridyl)piperazine, 4-(2-aminoethyl)morpholine, 1-(2-aminoethyl)piperidine, 3-aminopropipnitrile, 3-(aminomethyl)pyridine, 2-(aminomethyl)pyridine, thiomorpholine, 1,4-dioxa-8-azaspiro(4,5)-decane, 2-

hydroxylethylamine, 1-(2-aminoethyl)pyrrolidine, aminomethylcyclohexane, 2-hydroxymethylpyrrolidine, 3-amino-1,2-propanediol acetone ketal, N-(2-hydroxyethyl)piperazine, N-phenylethylenediamine, 4-amino-2,2,6,6-tetramethylpiperidine, N-(4-nitrophenyl)ethylenediamine, 1,2-diphenylethylamine, 1-(N,N-dimethylamino)-2-propylamine, 2-phenylpropylamine, 2-methylcyclopropylamine, 2-methylaziridine, aminomethylcyclopropane, 1-aminomethyl-2-methylcyclopropane, butten-3-ylamine, 3-methyl-buten-2-ylamine, 3-methyl-buten-3-ylamine, 4-aminomethyl-1-cyclohexene, 3-phenylallylamine, 2,2-dimethylethylenediamine, 3-ethylhexylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methyl-N-aminopropylpiperidine, as well as other related aliphatic and aromatic primary and secondary amine, hydrazine, hydroxyamine, various amino acid, amino acid ester derivatives that are good nucleophiles to react with leaving groups on the scaffolds.

Exemplary Building Blocks for C-C Bond Formation

For Heck Reaction: 2-ethynylpyridine, 5-phenyl-1-pentyne, 4-(tert-butyl)phenylacetylene, phenylacetylene, 3-dibutylamino-1-propyne, phenyl propargyl ether, 5-chloro-1-pentyne, 3-diethylamino-1-propyne, 4-phenyl-1-butyne, 1-heptyne, 1-dimethylamino-2-propyne, 1-pentyne, 2-methyl-1-hexene, (triethylsilyl)acetylene, 3-phenyl-1-propyne, methyl propargyl ether, 3-cyclopentyl-1-propyne, 1-ethynylcyclohexene, 3-butyn-1-ol, styrene, vinylcyclohexane, 2-(tributylstannyl)furan, 2-(tributylstannyl)thiophene, tetraphenyltin, 3-cyclohexyl-1-propyne, 4-methoxyphenylacetylene, 4-(trifluoromethyl)phenyleneacetylene, 4-fluorophenylacetylene, 4-pentayn-1-ol, 4-methylphenylacetylene, 1-ethynylcyclopentanol, 3-methyl-1-propyne, 5-cyano-1-pentyne, cyclohexylethyne, 1-ethynylcyclohexene, 5-cyano-1-pentyne, 1-dimethylamino-2-propyne, N-methyl-N-propargylbenzylamine, 2-methyl-1-buten-3-yne, cyclopentylethyne, 4-nitrophenylacetylene, phenyl propargylsulfide, 4-methyl-1-pentyne, propargyl ethylsulfide, 2-prop-2-ynyloxybenzothiazole, 4-ethoxy-1-prop-2-ynyl-1,5-dihydro-2H-pyrrol-2-one, 6-methyl-5-(2-propynyl)-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone and related end-alkenes and alkynes.

For Stille Reaction: tetraethyltin, 2-(tributylstannyl)pyridine, tributylstannyl-4-t-butylbenzene, ethynyltri-n-butyltin, vinyltri-n-butyltin, allyltri-n-butyltin, phenylethynyltri-n-butyltin, phenyltri-n-butyltin, (2-methoxy-2-cyclohexen-1-yl)tributyltin, 5,6-dihydro-2-

(tributylstannyl)-4H-pyran, tri-n-butyl(2-furanyl)tin, tri-n-butyl(2-thienyl)tin, tributyl(phenylethenyl)tin, 4-fluoro-(tri-n-butylstannyl)benzene, 5-fluoro-2-methoxy(tri-n-butylstannyl)benzene, 1-methyl-2-(tributylstannyl)-1H-pyrrole, 5-methyl-2-tributylstannylthiophene, 2-tributylstannylthiazole, 2-trybutylstannylpyrrazine, tributyl[3-(trifluoromethyl)phenyl]stannane and other related organic tin reagents.

For Suzuki Reaction: phenylboronic acid, 4-tolylboronic acid, 2-thiopheneboronic acid, thiophene-3-boronic acid, furan-2-boronic acid, cyclopentylboronic acid, 4-methylfuran-2-boronic acid, 3-hydroxyphenyl)boronic acid, 5-methylfuran-2-boronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, (5-formyl-3-furanyl)boronic acid, furan-3-boronic acid and other related organic boronic acids.

Exemplary Building Blocks ROH for Mitsunobu Reaction

1-Butanol, 4-nitrophenethyl alcohol, 4-chlorobenzyl alcohol, 1-propanol, 4-nitrobenzyl alcohol, 4-methylbenzyl alcohol, 2-butanol, benzyl alcohol, 2-methyl-1-propanol, crotyl alcohol, 2-norbornanemethanol, 2-methylcyclopropane-methanol, 3-buten-1-ol, neopentyl alcohol, cyclohexylmethanol, 4-trifluorobenzyl alcohol, 3-methyl-2-butem-1-ol, cyclopentanemethanol, 3-methyl-3-buten-1-ol, 4-methyl-1-pentanol, 3-chlorobenzyl alcohol, 3-cyclohexane-1-methanol, 3,3-dimethylbutanol, 3-trifluorobenzyl alcohol, cinnamyl alcohol, tetrahydrofurfuryl alcohol, ethanol, cyclopropyl alcohol, 1-methyl-3-piperidinemethanol, decahydro-2-naphthol, 9-decen-1-ol, 3-cyclopentyl-1-propanol, 1-methyl-2-pyrrolidineethanol, 3-methylbenzyl alcohol, 3-fluorobenzyl alcohol, 3-phenoxybenzyl alcohol, 4-isopropylbenzyl alcohol, 4-methoxybenzyl alcohol, 3,4-dimethoxybenzyl alcohol, 3,5-dimethylbenzyl alcohol, 4-benzyloxybenzyl alcohol, 2-phenylethanol, 4-fluorobenzyl alcohol, phenoxyethanol, benzyloxyethanol, 1-pentanol and 3-pentanol as well as aliphatic/aromatic/heterocyclic primary and secondary alcohols. Similar RSH derivatives have been used as building blocks for library synthesis.

All available aliphatic, aromatic and heterocyclic acyl chlorides, sulfonyl chlorides, isocyanates, thioisocyanates, carboxylic acids, amino acids, isocyanides, halogenated heterocycles for 2'- and 3'-NH_2 reactions.

BIOLOGICAL ASSAYS

The inventors discovered that various contemplated compounds exhibited significant antiviral effect, and especially significant antiviral effect against HCV in vitro and as NS5B inhibitors (data not shown). The assays used to measure the inhibition of HCV NS5B and other polymerases, in vitro cell-based HCV replication, BVDV, HIV, RSV, HRV, HBV, influenza, and cytotoxicity are described below.

Assay of De Novo RNA Synthesis Activity for HCV NS5B Polymerase

All the oligoribonucleosides were purchased from Oligo etc. and were gel-purified. All the chemical reagents were of highest purity possible. H_2O used in the assay was RNase and DNase free. [α-^{33}P]-CTP (Ci/mmol) was purchased from ICN Biochemicals or Perkin-Elmer.

A typical assay reaction was carried out at 23°C for one hour in a buffer containing 20 mM Tris, pH 8.0, 20 mM MgCl2, 10 mM KCl, 5 % Glycerol, 5 mM DTT and 0.5 mg/ml BSA. The template concentration was set at 10 mM and the enzyme concentration at 5 mM. The reaction was quenched by addition of a loading buffer (80% formamide, 100 mM EDTA, 50 mM Tris borate, 0.15% bromophenol blue and 0.15% of xylene cyanol) and heated to 70°C for 1 min prior to loading on a 1 X TBE polyacrylamide gel. Electrophoresis was performed in 1 X TBE at 3000 Volt. Gels were visualized and analyzed by using a PhosphorImager. Unless indicated otherwise, data are not shown for contemplated compounds.

HCV Replicon Assay

The replicon cells (Huh-7) contain replicating HCV replicon RNA, which was modified in the structural region (replacing the structural region with a neomycin resistance marker). Survival of the replicon cells under G418 selection relies on the replication of HCV RNA and subsequently expression of neomycin phosphoryltransferase. The ability of modified nucleoside libraries and compounds to suppress HCV RNA replication was determined using the Quantigene Assay Kit from Bayer. The assay measures the reduction of HCV RNA molecules in the treated cells. Replicon cells were incubated at 37°C for 3 days in the presence of nucleoside libraries and compounds before being harvested for detection. The

HCV subgenomic replicon cell line was provided by Dr. Bartenschlager. The assay protocol was modified based on literature procedure (V. Lohmann, F. Korner, J. O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, *Science*, **1999**, *285*, 110-113). Unless indicated otherwise, data are not shown for contemplated compounds.

Assay for Inhibition of BVDV

Bovine viral diarrhea virus (BVDV) (strain NADL) was provided by Dr. Ruben Donis and propagated in MDBK cells (ATCC). The nucleoside libraries and compounds were tested utilizing the modified protocol (V. B. Vassilev, M. S. Collett, R. O. Donis, *J. Viol.* **1997**, *71*, 471-478; S. G. Bagginski, D. C. Pevear, M. Seipel, S. C. C. Sun, C. A. Benetatos, S. K. Chunduru, C. M. Rice, M. S. Collett, *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7981-7986). Unless indicated otherwise, data are not shown for contemplated compounds.

Hepatitis B Virus (HBV) Assay

The in vitro anti-HBV activity of nucleoside libraries and compounds was tested based on the reported protocol (W. E. Delaney, 4th, R. Edwards, D. Colledge, T. Shaw, J. Torresi, T. G. Miller, H. C. Isom, C. T. Bock, M. P. Manns, C. Trautwein, S. Locarnini, *Antimicrob. Agents Chemother.*, **2001**, *45*, 1705-1713; W. E. Delaney, 4th, T. G. Miller, H. C. Isom, *Antimicrob. Agents Chemother.*, **1999**, *43*, 2017-2026; B. E. Korba, J. L. Gerin, *Antiviral Res.*, **1992**, *19*, 55-70). Unless indicated otherwise, data are not shown for contemplated compounds.

Human Immunodeficiency Virus (HIV) Assay

The in vitro HIV-1 activity of nucleoside libraries and compounds was tested utilizing the following modified protocol. Freshly isolated human PBMCs from healthy donors were infected with HIV-1 isolates for 3 hours. The cells were then washed three times to remove the viruses. The infected cells were plated into 96-well tissue culture plates and incubated for 7 days in the presence of serially diluted nucleoside analogues (with a medium change at day 4). A standardized HIV-1 p24 Elisa was performed to measure the extent of HIV replication in the presence of the compounds. (C. J. Petropoulos, N. T. Parkin, K. L. Limoli, Y. S. Lie, T. Wrin, W. Huang, H. Tian, D. Smith, G. A. Winslow, D. J. Capon, J. M. Whitcomb, *Antimicrob. Agents Chemother.*, **2000**, *44*, 920-928; Parkin, N. T., Y. S. Lie, N. Hellmann,

M. Markowitz., S. Bonhoeffer, D. D. Ho, C. J. Petropoulos, *J. Infect. Disease*, **1999**, *180*, 865-870). Unless indicated otherwise, data are not shown for contemplated compounds.

Human Rhinovirus (HRV) Assay

The in vitro activity of nucleoside libraries and compounds against HRV was tested based on the reported protocol (W.-M. Lee, W. Wang, R. Rueckert, *Virus Genes*, **1994**, *9*, 177-181; B. Sherry, R. Rueckert, *J. Virol.* **1985**, *53*, 137-143). Unless indicated otherwise, data are not shown for contemplated compounds.

Respiratory Syncytial Virus (RSV) Assay

The RSV activity of nucleoside libraries and compounds was tested based on the reported protocol. Respiratory syncytial virus (strain A-2) was purchased from ATCC and virus stock was obtained by propagating the virus in Hep-2 cells. (P. R. Wyde, L. R. Meyerson, B. E. Gilbert, *Drug Dev. Res.* **1993**, *28*, 467-472). Unless indicated otherwise, data are not shown for contemplated compounds.

Yellow Fever Virus (YFV) Assay

Yellow fever virus (vaccine strain 17-D) was purchased from ATCC (VR-1268) and the virus stock was obtained by infecting SW-13 cells from ATCC. The YFV activity of nucleoside libraries and compounds was tested utilizing the reported protocol (J. J. Schlesinger, S. Chapman, A. Nestorowicz, C. M. Rice, T. E. Ginocchio, T. J. Chambers, *J. Gen. Virol.* **1996**, *77*, 1277-1285). Unless indicated otherwise, data are not shown for contemplated compounds.

Influenza Virus Assay

Influenza virus (type A, A/PR/8/34) was produced by infecting pathogen-free fertilized chicken eggs. The antiviral assay was performed on Madin Darby canine kidney (MDCK) cells from ATCC based on the reported protocol (E. H. Nasser, A. K. Judd, A. Sanchez, D. Anastasion, D. J. Bucher, *J. Virol.* **1996**, *70*, 8639-8644). Unless indicated otherwise, data are not shown for contemplated compounds.

Cytotoxicity Assay

The cytotoxicity of nucleoside libraries and compounds was measured by the MTS cell based assay from Promega (CellTiter 96 Aqueous One Solution Cell Proliferation Assay). Unless indicated otherwise, data are not shown for contemplated compounds.

Consequently, it is contemplated that the compounds according to the inventive subject matter may be employed in pharmaceutical compositions to treat various viral diseases. In an especially preferred aspect of the inventive subject matter, the inventors contemplate a method of inhibiting replication of a virus in which one or more of the compounds according to the inventive subject matter are provided. In a further step, the virus is presented with the compound(s) at a concentration effective to inhibit replication of the virus. The term "presenting the virus with a compound" as used herein broadly refers to all manners in which the virus or viral component is incubated with the compound.

For example, where the virus or viral component (particularly including a viral RNA dependent RNA polymerase) is in an *in vitro* system, presentation may comprise admixing the medium in which the virus or viral component is disposed with the compound. In another example, where the virus or viral component is in a cell (either in a cell culture, or *in vivo* in a hepatocyte in an infected liver of a mammal) it is contemplated that the step of presenting may include administration of a pharmaceutical composition comprising contemplated compounds to the organism in which the virus or viral component is disposed. Suitable pharmaceutical compositions may include oral, parenteral, transdermal, and various other known pharmaceutical compositions. Hence, in an especially preferred aspect, the virus is an HCV virus and is disposed within a cell (which is preferably a hepatocyte in a liver infected with the virus).

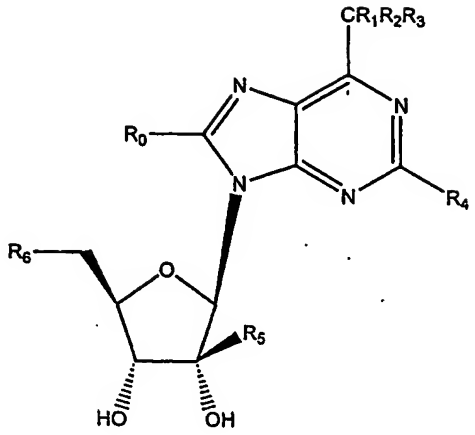
Thus, specific embodiments and applications of nucleoside analog libraries, library compounds and their use as antiviral agents have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements,

components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

CLAIMS

What is claimed is:

1. A compound according to Formula 1



Formula 1

wherein the sugar is in D- or L-configuration;

R_0 is H, or halogen, or optionally substituted alkyl, alkenyl, alkynyl, or aryl;

R_1, R_2, and R_3 are independently optionally substituted alkyl, alkenyl, alkynyl, aryl, or H, or where R_1 and R_2 are H, R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR', or alkyl-CN;

R_4 is H or NH_2;

R_5 is optionally substituted alkyl, alkenyl, alkynyl, aryl, or CN, or CF_3;

R_6 is H, OH, phosphate, phosphonate, or boranophosphate; and

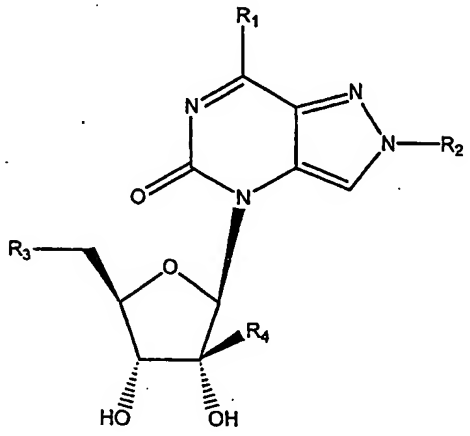
R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl.

2. The compound according to claim 1 wherein R_5 is methyl.

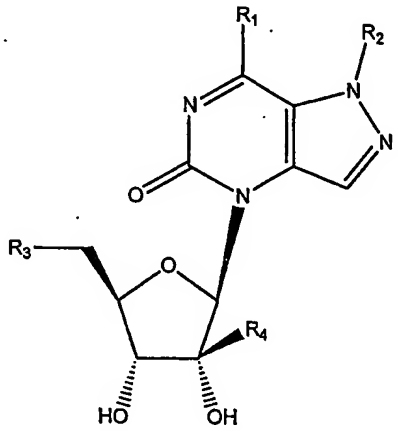
3. The compound according to claim 2 wherein R_6 is OH.

4. The compound according to claim 3 wherein R_0 is H, R_1 and R_2 are H, and wherein R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR'.

5. A compound according to Formula 2A or Formula 2B



Formula 2A



Formula 2B

wherein the sugar is in D- or L-configuration;

R_1 is NR'R", ONR'R", NR'NR'R", SR', OR', or R';

R_2 is alkyl, acyl, or aryl;

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, CN, or CF_3; and

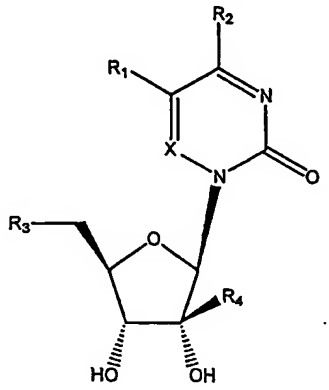
wherein R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl.

6. The compound according to claim 5 wherein R_4 is methyl and wherein R_3 is OH.

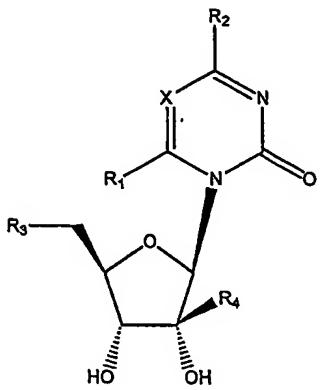
7. The compound according to claim 6 wherein R_1 is NR'R", ONR'R", or NR'NR'R".

8. The compound according to claim 6 wherein R_2 is alkyl.

9. A compound according to Formula 3A or Formula 3B



Formula 3A



Formula 3B

wherein the sugar is in D- or L-configuration;

X is N or CH;

R_1 is H, halogen, alkyl, or alkenyl;

R_2 is NR'R", ONR'R", NR'NR'R", SR', OR', or R';

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

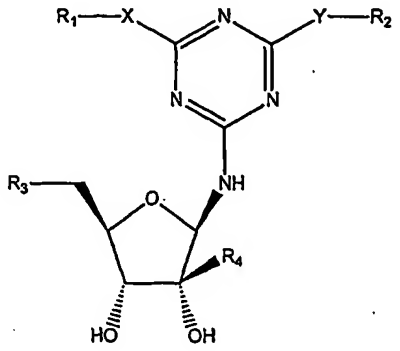
R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, CN, or CF_3; and

wherein R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl.

10. The compound according to claim 9 wherein R_4 is methyl and wherein R_3 is OH.

11. The compound according to claim 10 wherein R_1 is H and R_2 is NR'R", ONR'R", or NR'NR'R".

12. A compound according to Formula 4



Formula 4

wherein X and Y are independently null, NR', O or S;

R_1 and R_2 are independently NR'R" or H, or optionally substituted alkyl, alkenyl, alkynyl, or aryl;

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, or CN or CF_3; and

R' and R" are independently H or OH, or optionally substituted alkyl, alkenyl, alkynyl, or aryl.

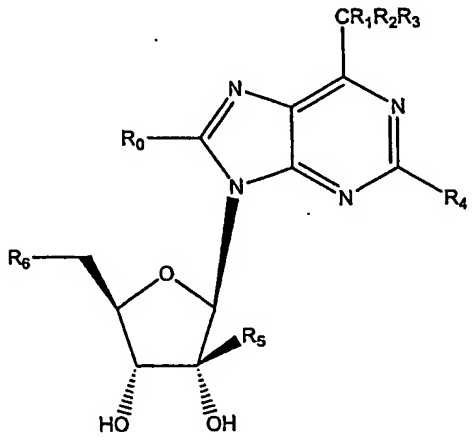
13. The compound according to claim 12 wherein R_3 is OH and R_4 is CH_3.

14. The compound according to claim 13 wherein X and Y are NR'.

AMENDED CLAIMS

[received by the International Bureau on 02 July 2003 (02.07.03);
original claims 1-14 replaced by new claims 1-14.]

1. A compound according to Formula 1



Formula 1

wherein the sugar is in D- or L-configuration;

R_0 is H, or halogen, or optionally substituted alkyl, alkenyl, alkynyl, or aryl;

R_1, R_2, and R_3 are independently optionally substituted alkyl, alkenyl, alkynyl, aryl, or H, or where R_1 and R_2 are H, R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR', or alkyl-CN;

R_4 is H or NH_2;

R_5 is optionally substituted alkyl, alkenyl, alkynyl, aryl, or CN, or CF_3;

R_6 is H, OH, phosphate, phosphonate, or boranophosphate; and

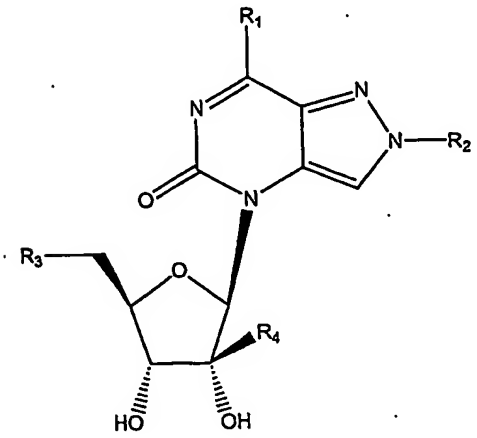
wherein R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl.

2. The compound according to claim 1 wherein R_5 is methyl.

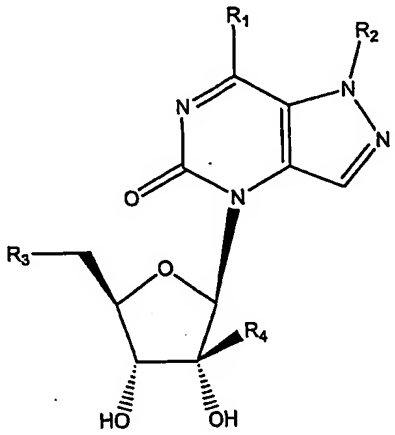
3. The compound according to claim 2 wherein R_6 is OH.

4. The compound according to claim 3 wherein R_0 is H, R_1 and R_2 are H, and wherein R_3 is alkyl-NR'R", alkyl-ONR'R", alkyl-NR'NR'R", alkyl-SR', alkyl-OR'.

5. A compound according to Formula 2A or Formula 2B



Formula 2A



Formula 2B

wherein the sugar is in D- or L-configuration;

R_1 is NR'R", ONR'R", NR'NR'R", SR', OR', or R';

R_2 is selected from the group consisting of alkyl, acyl, and aryl;

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, CN, or CF_3; and

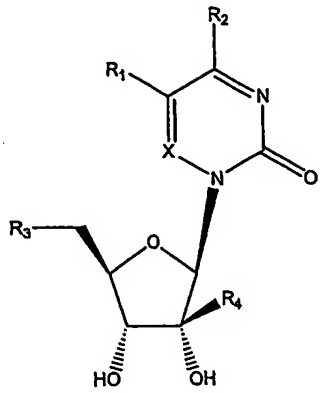
wherein R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl.

6. The compound according to claim 5 wherein R_4 is methyl and wherein R_3 is OH.

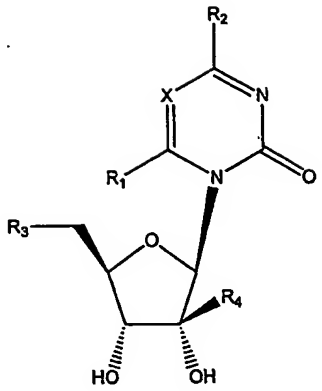
7. The compound according to claim 6 wherein R_1 is NR'R", ONR'R", or NR'NR'R".

8. The compound according to claim 6 wherein R_2 is alkyl.

9. A compound according to Formula 3A or Formula 3B



Formula 3A



Formula 3B

wherein the sugar is in D- or L-configuration;

X is N or CH;

R_1 is H, halogen, alkyl, or alkenyl;

R_2 is NR'R", ONR'R", NR'NR'R", SR', OR', or R';

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, CN, or CF_3; and

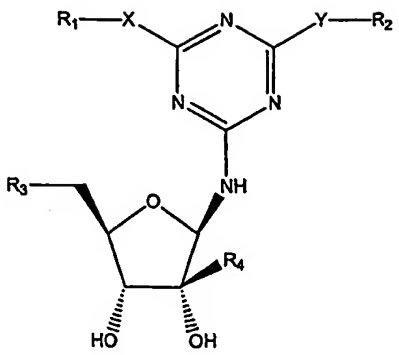
wherein R' and R" are independently H, OH, or optionally substituted alkyl, alkenyl, alkynyl, aryl; and

with the proviso that where in compounds according to Formula 3A X is CH and R_2 is NH_2, then R_1 is not H, Halogen, or alkyl.

10. The compound according to claim 9 wherein R_4 is methyl and wherein R_3 is OH.

11. The compound according to claim 10 wherein R_1 is H and R_2 is NR'R", ONR'R", or NR'NR'R".

12. A compound according to Formula 4



Formula 4

wherein X and Y are independently null, NR', O or S;

R_1 and R_2 are independently NR'R" or H, or optionally substituted alkyl, alkenyl, alkynyl, or aryl;

R_3 is protected or unprotected OH, phosphate, phosphonate, or boranophosphate;

R_4 is optionally substituted alkyl, alkenyl, alkynyl, aryl, or CN or CF_3; and

wherein R' and R" are independently H or OH, or optionally substituted alkyl, alkenyl, alkynyl, or aryl.

13. The compound according to claim 12 wherein R_3 is OH and R_4 is CH_3.

14. The compound according to claim 13 wherein X and Y are NR'.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/01557

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07H 19/00; A01N 43/04; A61K, 31/70
US CL : 536/26.1, 26.11, 26.12, 26.13, 27.21, 27.6, 27.62, 28.5; 514/45, 46, 47, 48, 49
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/26.1, 26.11, 26.12, 26.13, 27.21, 27.6, 27.62, 28.5; 514/45, 46, 47, 48, 49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, STN (REGISTRY, CAPLUS, MEDLINE, BIOSIS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/90121 A2 (NOVIRIO PHARMACEUTICALS LIMITED et al.) 29 November 2001 (29.11.2001).	1-14
X	WO 01/92282 A2 (NOVIRIO PHARMACEUTICALS LIMITED et al.) 6 December 2001 (06.12.2001).	1-14
X, P	WO 02/057425 A2 (MERCK & CO., INC. et al.) 25 July 2002 (25.07.2002).	1-14
X, P	WO 02/18404 A2 (F. HOFFMANN-LA ROCHE AG) 7 March 2002 (07.03.2002).	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 2003 (21.04.2003)	02 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer James O. Wilson Telephone No. (703) 308-1235

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